The Atrial Natriuretic Factor in Hypertension
State of the Art Lecture

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SUMMARY  Studies were conducted to assess the effects of bolus injections and infusions of human atrial natriuretic factor (ANF) in control subjects and patients with mild essential hypertension, and to measure plasma immunoreactive ANF (irANF) concentration in a large group of patients with essential hypertension. The results are compared with those obtained by other groups on the measurements of plasma irANF in hypertensive patients. It appears that plasma irANF concentrations are not increased in patients with mild essential hypertension despite the evidence of increased preload and of atrial distention as reported by others. This suggests a hyporesponsiveness of the atria to release ANF.

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KEY WORDS • atrial natriuretic factor • essential hypertension • atrial distention

The atrial natriuretic factor (ANF) released in plasma is a 28 amino acid peptide that represents the carboxyl end of a larger preprohormone of 151 amino acids in humans and 152 in rats. The prohormone of 128 amino acids is the form that is stored in the granules seen in most cardiocytes of both atria of mammals$^1$ and that, under the stimulus of pressure or stretch or both, is cleaved by a CRIM-serine protease-1 to liberate the active peptide.$^3$ Since its isolation and synthesis more than 3 years ago, all investigations in animals and humans have demonstrated that the peptide has important properties in relation to the regulation of blood pressure: 1) it produces selective vasodilatation in many arterial territories, especially aortic, renal, and carotid, by inhibiting and preventing the vasoconstrictor effects of norepinephrine and of angiotensin II; 2) it produces massive, rapid diuresis and natriuresis of short duration; 3) it decreases cardiac output; 4) it inhibits aldosterone synthesis and renin release; and 5) it produces a shift of fluids from the vascular space to the extravascular one.$^4$

These were the reasons that led the members of our group to study the effects of the intravenous administration of known ANF by bolus or continuous intravenous (i.v.) infusion and its plasma concentration in patients with essential hypertension.

Subjects and Methods

Plasma immunoreactive ANF (irANF) was measured by radioimmunoassay after extraction on Sep-Pak cartridges for human plasma.$^5$ $^6$ Human ANF (Ser 99-Tyr 126, Met 110) was purchased from Armand Frappier Productions (Montreal, Canada).

Control subjects were members and employees of our institute. A group of 101 patients with essential hypertension was studied. They were either untreated (20%) or had their medication discontinued at least 3 weeks before the study (80%). Twenty-five had labile essential hypertension and normal blood pressure at the time of blood sampling. Sixty-seven were patients with mild essential hypertension with diastolic pressures between 90 and 105 mm Hg, without left ventricular hypertrophy, and without target organ damage. Nine patients had diastolic pressures between 105 and 120 mm Hg. Sixteen patients were receiving antihypertensive medication without control of blood pressure, and their diastolic pressure at the time of blood sampling was above 110 mm Hg.

Another 40 hypertensive patients underwent renal angiography. Twenty-four had significant unilateral renal artery stenosis with markedly increased renal venous renin activity on the stenotic side.

Results and Discussion

Larochelle et al.$^7$ and Weil et al.$^8$ did not observe any increase of plasma irANF with age in control subjects, although Ohashi et al.$^9$ reported a significant

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increase in the older group (64–91 years of age) versus a younger group (24–29 years of age). Larochelle et al.\textsuperscript{7} found a very significant correlation of plasma irANF with age in hypertensive patients (Figure 1). This is in contrast with the findings of Richards et al.\textsuperscript{10} who noted a significant positive correlation of plasma irANF with age in normal subjects but not in hypertensive patients.

Bolus administration of ANF up to 25 \(\mu g\) i.v. in healthy volunteers had no effect on blood pressure, although plasma irANF reached peak levels of 367 pmol/L, or on diuresis and natriuresis, despite a significant increase in plasma cyclic guanosine 3',5'-monophosphate (cGMP). Only with a bolus of 50 \(\mu g\) i.v. and higher was there a significant decrease in both systolic and diastolic pressures of 8/8 mm Hg and greater, with peak plasma irANF levels above 400 pmol/L coinciding with marked diuresis and natriuresis and a significant increase in plasma cGMP levels.\textsuperscript{4,11,12} Similar results were obtained by others.\textsuperscript{13,14}

Intravenous infusions of ANF at 0.8, 1.6, and 3.2 \(\mu g/min\) for periods of 30 minutes each were administered to seven normal subjects and five patients with mild essential hypertension. With the highest infusion dose, plasma levels of irANF were between 77 and 83 pmol/L. No effect on blood pressure was noted despite a significant increase in diuresis and natriuresis.\textsuperscript{4,12,15} Weidmann et al.\textsuperscript{16} followed a similar protocol but administered ANF at 6.5 and 12.5 \(\mu g/min\) for 45 minutes. They observed a significant fall in blood pressure in 10 patients with essential hypertension from an average of 181/127 to 165/110 mm Hg, with an average plasma irANF concentration of 208 \pm 29 pmol/L. No change was noted in plasma renin activity, or aldosterone and angiotensin II levels, but a significant increase in plasma norepinephrine concentration was noted.

Plasma irANF concentration in 101 patients with essential hypertension was measured. The results obtained in patients with labile and with mild essential hypertension (diastolic pressures between 90 and 105 mm Hg) were identical to those obtained in control subjects (Figure 2). It is to be noted that, save for one patient, plasma levels in the 67 patients with mild essential hypertension were all below 13 pmol/L. Only in some patients with diastolic pressures between 105 and 120 mm Hg or with diastolic pressure above 110 mm Hg and poorly controlled despite antihypertensive medication was plasma irANF significantly increased.\textsuperscript{7} Identical results in a similarly defined group of patients with mild essential hypertension were obtained by Zachariah et al.\textsuperscript{17} As described in Table 1, six other groups could not find any significant difference in mean plasma irANF concentrations in patients with undefined hypertension as to type or severity.\textsuperscript{19–24} In all these studies, plasma irANF was measured after extraction with Sep-Pak cartridges, except for that of Yamaji et al.\textsuperscript{24} who used affinity chromatography on antiANF-coupled agarose for purification of plasma ANF.

On the other hand, in undefined groups of hypertensive patients, some researchers\textsuperscript{25–29,31} found plasma irANF levels (after Sep-Pak extraction) slightly but significantly higher in hypertensive patients as compared to control subjects. Similarly, Arendt et al.,\textsuperscript{30} using Amberlite XAD-2 resin for extraction of plasma ANF, reported significantly higher levels in an undefined group of hypertensive patients when compared to control subjects. In some of the undefined hypertensive groups, patients with moderate or severe hypertension, and possibly with some degree of congestive heart failure, were included.

Our results and those of others\textsuperscript{17} are consistent with the findings of Ogawa et al.\textsuperscript{22} and of Tsuchiga et al.\textsuperscript{23} They demonstrated that the plasma levels of cGMP, which is a marker of ANF activity, were not increased in 68 patients with essential hypertension when compared to control subjects.
From our studies and those of others, except those of Adrendt et al., it appears clear that plasma irANF must be higher than 83 pmol/L to exert any effect on blood pressure, and such levels were not found in any of the patients studied, even those with moderate and severe essential hypertension. It is also consistent with the recent findings of Zimmerman et al. that i.v. infusions of human ANF into pentobarbital-anesthetized dogs must be at rates sufficient (between 0.01 and 0.3 μg/kg/min) to raise the plasma levels between 94 ± 7 and 173 ± 12 pmol/L to produce any significant lowering of blood pressure. This led us to interpret our findings as indicating a hyporesponsiveness of the atria to release ANF. This hypothesis is reinforced by the finding of several workers of high right and left atrial pressures and atrial distention in patients with mild and moderate essential hypertension compared to control subjects.

Ferlinz evaluated 20 patients with mild and moderate essential hypertension with mean systolic and diastolic pressures of 166 ± 23/92 ± 11 mm Hg. They experienced an increase of 3 mm Hg in mean pulmonary capillary wedge and right atrial pressures in comparison to the findings in 10 normotensive subjects. Similarly, London et al. reported on 49 patients with essential hypertension with mean arterial pressures of 179 ± 3.6/106 ± 2.1 mm Hg. They noted a significant increase in mean right atrial pressure (1.9 mm Hg) and pulmonary capillary wedge pressure (3.7 mm Hg) in these patients in comparison to a group of 27 normotensive subjects.

Our hypothesis of specific hyporesponsiveness of the atria in patients with mild essential hypertension to release ANF is consistent with 1) the reported normal plasma levels of cGMP, which is a marker of ANF activity; 2) the decreased ability of the hypertensive kidney to excrete sodium loads, as postulated by Guyton et al. unless by increasing the blood pressure (pressure natriuresis), as demonstrated in rats by Tobian et al.; 3) the decreased inhibition of aldosterone secretion and the inappropriately high levels of secretion, plasma levels, and excretion of aldosterone in patients with essential hypertension during high sodium intake, as demonstrated by Collins et al.; and 4) the increased peripheral resistance characteristic of essential hypertension because of the insufficient concentration of circulating ANF to prevent or to decrease the vasoconstrictor activity associated either with norepinephrine or with angiotensin II.

Plasma irANF was slightly but significantly elevated in aortic blood, but not increased in peripheral blood of 24 patients with renovascular hypertension. Nor was there any difference in plasma irANF measured directly in renal venous blood of both kidneys in these patients, despite a significant increase in plasma renin activity in the renal venous blood of the stenotic kidney.

**Conclusion**

It appears from our own data and from a review of the literature that the evidence available in patients with mild essential hypertension shows no significant increase in plasma irANF concentration, on the basis of actual measurements as well as the findings of normal plasma cGMP levels. In view of the greater pres-
sures and distention reported by other workers in both right and left atria in patients with mild and moderate essential hypertension, an atrial hyporesponsiveness to release ANF is postulated. Work is actually in progress to measure simultaneously plasma irANF and cGMP, as well as the pressures in the right atrium and the pulmonary capillary wedge pressure in patients with well-established mild essential hypertension.

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