The effect of treatment of congestive heart failure on plasma atrial natriuretic peptide concentration: a longitudinal study

J V ANDERSON, P W R WOODRUFF,* S R BLOOM

From the Departments of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital; and King's College Hospital, Denmark Hill, London*

SUMMARY Eleven patients with acute congestive heart failure were studied during treatment with a loop diuretic. Plasma concentrations of atrial natriuretic peptide were considerably increased before treatment and with successful treatment returned progressively towards normal values. There was a statistically significant correlation between plasma atrial natriuretic peptide concentration and both jugular venous pressure and change of body weight.

These results support the hypothesis that atrial distension is an important stimulus to atrial natriuretic peptide release. Furthermore, the close relation between plasma concentrations of atrial natriuretic peptide and clinical improvement in these patients suggests that measurement of plasma atrial natriuretic peptide concentration could provide a clinically useful and non-invasive method of monitoring the response to treatment.

Soon after the discovery that high concentrations of peptides with potent natriuretic properties are stored in atrial muscle cells,¹ it was proposed that atrial distension caused by changes of extracellular fluid volume might act as a stimulus to the release of atrial natriuretic peptide into the circulation, and that atrial natriuretic peptide could thus act as a natriuretic hormone.² The intravenous infusion of sufficient quantities of saline or colloid to raise atrial pressure has been shown to produce a dose dependent plasma release of atrial natriuretic peptide in laboratory animals^{3,4} and human beings.⁵ Several cross sectional studies have shown a relation between atrial pressure and plasma atrial natriuretic peptide concentration during cardiac catheterisation procedures.⁶⁻⁸

We report the results of a longitudinal study to assess the changes in the plasma concentration of atrial natriuretic peptide before and during the treatment of patients with acute exacerbations of congestive heart failure.

Patients and methods

PATIENTS

Eleven consecutive patients (aged 39-84, mean 69) with acute exacerbations of congestive heart failure were studied. Table 1 shows their diagnoses, drug treatment, and further clinical details. Inclusion criteria for the study were (a) a history of increasing breathlessness and orthopnoea; (b) clinical signs of an elevated jugular venous pressure and peripheral and pulmonary oedema; (c) radiological evidence of left heart failure. Patients who required mechanical ventilation, were too ill to be managed on a general medical ward, or who had evidence of valvar heart disease were excluded. All patients gave their consent to the study which was approved by the hospital ethics committee.

Any previous diuretic treatment was stopped on admission but all other medications were continued unchanged. The patients were treated with doses of frusemide (and oral potassium supplements) adjusted to the clinical response. In all cases the jugular venous pressure and body weight were measured and blood samples were taken on admission and thereafter at a similar time of day (either between 10.30 and 11.30 am or between 3.30 and 5.30 pm) on at least four further occasions. Venous pressure

Requests for reprints to Professor S R Bloom, Francis Fraser Laboratories, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London W12 0HS.

Table 1 Clinical details of the patients studied

Patient	Sex	Age	Medications on admission to hospital (daily dose)	Aetiology of current episode of heart failure	Duration of present symptoms	Previous illnesses (year of onset)	Symbol used in fig 1
1	M	68	Salbutamol inhaler, methyldopa (1.5 g), aminophylline (450 mg), frusemide (120 mg), slow release K ⁺	IHD; poor compliance	7 days	Hypertension (1963), chronic bronchitis (1975), myocardial infarct (1978), retinal detachment (1978), recurrent admissions CHF (1978)	▲
2	M	39	Thiamine (100 mg), digoxin (0.25 mg), prazosin (6 mg)	Alcoholic cardiomyopathy	2 weeks	Nil	●
3	F	84	Digoxin (0.0625 mg), isosorbide dinitrate (80 mg), frusemide (40 mg)	Myocardial infarct	3 weeks	Myocardial infarct (1977), atrial fibrillation (1981)	★
4	F	74	Allopurinol (300 mg), warfarin (4 mg), frusemide (80 mg), slow release K ⁺	IHD	3 days	Anterior myocardial infarct (1972), transient ischaemic attack (1976), gout (1981)	○
5	M	78	Aldactide* (2 tab)	Alcoholic cardiomyopathy	4 days	CHF (1985)	▼
6	F	78	Allopurinol (300 mg), moduretic* (2 tab), digoxin (0.125 mg)	IHD, atrial fibrillation	3 weeks	Hypertension (1964), breast cancer (1967), atrial fibrillation (1971), gout (1984)	▽
7	M	64	Isosorbide dinitrate (40 mg), nifedipine (40 mg), frusemide (120 mg)	Myocardial infarct	1 day	Hypertension (1962), myocardial infarct (1977), stroke (1977), recurrent CHF (1982), angina (1984)	△
8	F	64	Aminophylline (450 mg), frusemide (80 mg)	Cor pulmonale	3 days	Chronic bronchitis (1965)	◇
9	M	74	Isosorbide mononitrate (20 mg), salbutamol (4 mg), digoxin (0.125 mg), frusemide (40 mg), spironolactone (100 mg)	IHD, atrial flutter	2 weeks	Chronic bronchitis (1971), hypertension (1982), intermittent claudication (1982), angina (1984), CABG (1984)	◆
10	M	76	Digoxin (0.0625 mg), frusemide (80 mg), amiloride (5 mg)	IHD, atrial fibrillation	3 weeks	CHF (1985), atrial fibrillation (1985)	■
11	M	70	Thyroxine (50 µg), frusemide (40 mg)	Hypothyroidism, IHD	2 weeks	Myocardial infarct (1984)	□

IHD, ischaemic heart disease; CHF, congestive heart failure; CABG, coronary artery bypass graft.

measurements and blood sampling were performed with patients in bed supported at 45° on pillows. Venous pressure was measured visually at the bedside on a vertical centimetre scale to judge the height of the jugular venous pulsation above the angle of Louis.

Observations were continued until the physician in charge of each patient judged on clinical grounds that the patient was fit enough to be discharged from hospital and to continue treatment at home.

BLOOD SAMPLING PROCEDURE AND RADIOIMMUNOASSAY OF ATRIAL NATRIURETIC PEPTIDE

Blood samples (12 ml) were taken into glass tubes containing 60 mg of potassium EDTA and 4000 kallikrein inactivator units of aprotinin (Trasylol, Bayer Pharmaceuticals). The tubes were stored on

ice and then centrifuged within 15 minutes of venesection. The plasma was separated and frozen at -20°C until assay. After thawing, atrial natriuretic peptide was extracted from 3 ml volumes of plasma on Sep-pak C18 cartridges (Waters Associates) by a procedure with a mean (SEM) extraction recovery of 79 (2)%.⁹ The extracts were evaporated to dryness in a Savant vacuum centrifuge and the pellet was dissolved in 1.2 ml of radioimmunoassay buffer overnight. Volumes (400 µl, 100 µl, and 25 µl) of the reconstituted extracts were assayed in duplicate by a specific radioimmunoassay (using antibody Y2) developed at the Royal Postgraduate Medical School that was capable of detecting 1 pmol/l changes of atrial natriuretic peptide concentration from zero with 95% confidence.^{9,10} The plasma atrial natriuretic peptide concentration was not corrected for extraction recovery.

Data are given both as actual values for each individual patient during the course of treatment and as mean (SEM) for all patients at specific time points during treatment. Statistical analysis was by Student's *t* test. Correlation coefficients were calculated by the linear regression technique.

Results

In all patients the jugular venous pressure was considerably elevated and plasma atrial natriuretic peptide concentration was raised on admission and returned progressively towards normal with diuretic treatment (figs 1, 2, and 3). There was a highly significant difference between the initial (80.7 (16.0) pmol/l) and final (18.5 (3.2) pmol/l) mean values of the plasma atrial natriuretic peptide concentration ($p < 0.001$), jugular venous pressure (initial 8.3 (0.8) and final 2.3 (0.4) cm H₂O, $p < 0.001$) and change of body weight (7.1 (1.8) kg, $p < 0.001$). The time course of the return of the mean plasma atrial natriuretic peptide concentration towards normal

Fig 1 Mean (SEM) values of plasma atrial natriuretic peptide concentration during diuretic treatment of congestive heart failure for one week in 11 patients. The broken line indicates the upper limit (15 pmol/l) of the normal 9 am fasting plasma atrial natriuretic peptide concentration in recumbent healthy young adults ($n = 24$).¹⁰

Fig 2 Mean (SEM) values of loss of body weight during diuretic treatment of congestive heart failure for one week in 11 patients.

values closely paralleled that of both the mean jugular venous pressure and the mean change of body weight (fig 1). Plasma atrial natriuretic peptide concentration showed a close correlation with jugular venous pressure both within individuals (table 2) and within

Table 2 Relation between serial measurements of plasma atrial natriuretic peptide and jugular venous pressure in individual patients

Patient	Slope	Intercept	Correlation coefficient (<i>r</i>)	Probability of nul hypothesis (<i>p</i>)
1	5.0	7.2	0.99	0.001
2	9.8	1.2	0.74	0.01
3	6.0	9.4	0.95	0.05
4	9.3	9.4	0.95	0.05
5	8.0	16.5	0.60	0.12
6	7.4	21.5	0.97	0.05
7	17.5	22.7	0.96	0.01
8	3.7	0.6	0.95	0.001
9	6.2	1.5	0.86	0.01
10	14.7	5.0	0.89	0.05
11	20.0	19.4	0.99	0.01

Fig 3 Mean (SEM) values of jugular venous pressure during diuretic treatment of congestive heart failure for one week in 11 patients.

the group as a whole ($r = 0.62$, $p < 0.001$). Similarly within the group plasma atrial natriuretic peptide concentration correlated significantly with body weight ($r = 0.59$, $p < 0.01$). A similar pattern of response to treatment was seen irrespective of the aetiology of the congestive heart failure.

Discussion

Soon after the isolation, sequencing, and synthesis of the atrial peptides, Sagnella and MacGregor postulated that atrial natriuretic peptide was a natriuretic hormone and that atrial distension was a major stimulus to atrial natriuretic peptide release.² Evidence supporting this hypothesis includes that of Lang and his colleagues who showed that raising the filling pressure of an isolated heart preparation increased atrial natriuretic peptide release from the heart.⁴ Expansion of blood volume with colloidal solution has been shown to release atrial natriuretic peptide into plasma *in vivo*.³ More recently in human beings, saline infusion was shown to cause the release of atrial natriuretic peptide into plasma.^{5,11} Furthermore, the increase of plasma atrial natriuretic peptide concentration in response to saline infusion correlates closely with changes of right atrial pressure.⁵ These studies support Sagnella and MacGregor's hypothesis.

Acute heart failure increases atrial filling pressures and might thus be expected to release increased quantities of atrial natriuretic peptide into plasma. Previous brief reports have described raised plasma

atrial natriuretic peptide concentrations in patients with congestive heart failure,¹²⁻¹⁴ and the results of cross sectional studies have supported the presence of a link between atrial pressure and atrial natriuretic peptide release.⁶⁻⁸ The present study goes further and demonstrates a close relation between clinical indices of the severity of heart failure (serial measurement of the jugular venous pressure and of body weight) and circulating concentrations of atrial natriuretic peptide when individual patients are studied longitudinally.

We studied patients presenting consecutively for emergency treatment in hospital and we used specific but broad selection criteria so that our findings would be relevant to routine clinical practice. In this group of patients there was naturally some variation in drug treatment and in the aetiology of the heart failure. The fact that this variability did not prevent a clear relation between the observed indices of the clinical severity of the heart failure and the circulating concentrations of atrial natriuretic peptide from emerging reinforces the general applicability of our observation.

We have shown that plasma concentrations of atrial natriuretic peptide are raised for some days as a result of acute congestive heart failure. The pathophysiological importance of this finding remains to be explained. Clearly the high concentrations of atrial natriuretic peptide were not causing a diuresis and natriuresis of sufficient magnitude to alleviate the condition spontaneously. This may be due in part to the activation of the sodium-conserving renin-angiotensin-aldosterone system that is known to occur in heart failure.^{15,16}

Acute congestive heart failure produces sustained increases of atrial pressure. Monitoring of atrial pressure can provide an important guide to clinical management.¹⁷ Thus we speculate that if circulating concentrations of atrial natriuretic peptide are indeed related to atrial distension, as the present study would suggest, monitoring of the plasma atrial natriuretic peptide concentration could provide a clinically useful non-invasive index of the response to treatment. Despite the intense medical and scientific interest generated by the discovery of atrial natriuretic peptide,^{18,19} little information of direct relevance to the general physician has so far emerged. We therefore feel that this speculative hypothesis warrants further clinical investigation.

Currently clinical application of plasma atrial natriuretic peptide assays would be limited by the need for plasma extraction and relatively long assay incubation times. The assay used in this study had a two day extraction step followed by a four day incubation. Overnight assay incubation gives acceptable, reproducible, and adequately sensitive (2 fmol/

assay tube) results for patient monitoring. Clearly a goal for the near future is a further reduction in assay times. Radioreceptor assays are already being developed with incubation times of a few hours only²⁰ and further advances in atrial natriuretic peptide assay technology can be expected.

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