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Neuroendocrine activity in untreated heart failure

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Abstract

Neuroendocrine activity was studied in 60 consecutive untreated patients with dyspnoea and a clinical suspicion of heart failure. On the basis of the so-called Boston clinical criteria the diagnosis of heart failure was regarded as unlikely in 26 patients, possible in 15 patients, and definite in 19 patients. These groups were studied before any drug treatment was started and were compared with a control group of 69 healthy individuals. Plasma atrial natriuretic peptide concentration was clearly raised in patients with definite heart failure and slightly raised in patients with possible heart failure. Plasma adrenaline concentration was somewhat raised in patients with definite or possible heart failure, whereas plasma noradrenaline concentration was raised only in patients with definite heart failure. Plasma renin activity was not increased in any of the patient groups and plasma aldosterone concentration was slightly increased only in patients with definite heart failure. In the total patient series there were significant correlations between plasma atrial natriuretic peptide concentration and markers of the severity of left ventricular dysfunction.

There was some evidence of neuroendocrine activation in untreated heart failure: plasma concentrations of atrial natriuretic peptide and catecholamines were increased but the renin-angiotensin-aldosterone system showed little or no activation.

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The basic disturbance in heart failure is a defect in left ventricular pump function which results in inadequate blood flow to peripheral tissues. In advanced congestive heart failure, complex neuroendocrine mechanisms are activated in an attempt to compensate for the decreased cardiac output. These responses include release of atrial natriuretic peptide from cardiac myocytes,[1–3] activation of the sympathetic nervous system,[4 5] and activation of the renin-angiotensin-aldosterone system.[6–8]

Most studies of the hormonal changes in heart failure have included patients treated with diuretics; there is little information on the activation of the neuroendocrine system in untreated heart failure,[9–12] especially on concentrations of atrial natriuretic peptide. We studied neuroendocrine activation in patients in whom the diagnosis of heart failure was suspected for the first time and in whom treatment for the condition had not been started. We used the Boston diagnostic criteria[13] to confirm the clinical diagnosis of heart failure.

Patients and methods

PATIENTS

We studied 88 patients (37 men and 51 women) with a clinical suspicion of previously unrecognised heart failure and 82 controls (36 men and 46 women), all aged 45–74 years. Patients were identified by 32 primary health care physicians working in community health centres in a defined area in eastern Finland. These physicians had agreed to refer to the university clinic all patients who had presented with symptoms or signs suggestive of heart failure and in whom this condition had not been previously diagnosed. Patients with acute pulmonary oedema complicating myocardial infarction were not included. Those 24 patients who had severe symptoms were referred immediately and studied on the day of referral, whereas the remaining 64 patients with milder symptoms were examined within two weeks of their visit to the primary health care centre. A detailed description of the patient series has been published elsewhere.[14]

Twenty eight patients were excluded from hormone analyses: 21 because of current treatment with digitalis, diuretics, angiotensin converting enzyme inhibitors, or sympathomimetic drugs; three because of severe respiratory failure caused by pulmonary disease or kyphoscoliosis, and four because of other diseases with indications for immediate treatment such as acute bronchitis, acute fibrosing alveolitis, diabetic ketoacidosis, or pulmonary embolism. Thus 60 patients (23 men and 37 women) comprised the final patient population. All of them had dyspnoea or fatigue or both. Seven patients had atrial fibrillation and 53 were in sinus rhythm.

We identified 300 candidates for the control group by a random population sample of 45–74 year old inhabitants in the survey area. A mailed questionnaire was used to exclude persons with previously diagnosed heart failure, coronary heart disease, hypertension, arrhythmias, or other disabling conditions. Eighty eight persons were thus selected from the initial sample, but 19 of them were excluded after the study visit. The reasons for exclusion

were bronchial asthma, coronary heart disease (15 cases), gastric carcinoma, hypertrophic cardiomyopathy, and Parkinson's disease. Thus the control group comprises 69 persons without any symptomatic cardiac or pulmonary disease or other obvious disease.

All examinations at the Kuopio University Central Hospital were performed before drug treatment for heart failure was started. The study was carried out from 1 June 1986 to 3 May 1988 and the patient and control series were examined in parallel over the study period. The study protocol was approved by the ethics committee of the University of Kuopio. Informed consent was obtained from each patient and control.

Methods

Clinical examination

One of us (JR) carried out the clinical examination and interpretation of conventional chest radiographs on all study subjects. The examination included a questionnaire on the patient's history of previous diseases and use of drugs. At the physical examination special attention was paid to signs of heart failure, such as the third heart sound, rales or wheezing on lung auscultation, raised jugular venous pressure, liver enlargement, or leg oedema. Weight and height were measured in light indoor clothing and body mass index was calculated as weight in kilograms per height in metres squared. A patient was considered to be non-obese if body mass index was <27 kg/m^2 and obese if body mass index was $\geqslant 27$ kg/m^2. Blood pressure was measured in recumbent individuals with a sphygmomanometer after five minutes of supine rest and the average of two measurements at an interval of two minutes was used. Heart rate was obtained from the resting electrocardiogram and relative heart volume was estimated from the chest x ray according to the method of Jonsell.[15]

Diagnostic classification

Information from clinical and radiographic examinations was used in the diagnostic classification of patients by a modification of the so-called Boston diagnostic criteria for heart failure.[13 14] In this scoring system points were given in three categories: for features in the history, for physical signs, and for radiographic signs suggestive of the presence of heart failure. Points were given in the first category for symptoms of dyspnoea and fatigue; in the second category for tachycardia, raised jugular venous pressure, lung rales or wheezing, and third heart sound; and in the third category for abnormal filling pattern of pulmonary veins, enlarged heart silhouette, pleural effusion, and evidence of interstitial or alveolar pulmonary oedema. A maximum of four points was allowed in each of the three categories, so a maximum score of 12 points was possible. Group 1 consisted of patients with a score of 0–4 points, defined as "unlikely to have heart failure". Patients with a score of 5–7 points were defined as having "possible heart failure" (group 2). Patients with a score of 8–12 points were defined as having "definite heart failure" (group 3).

A patient was considered to have coronary heart disease when one of the following criteria was fulfilled: (*a*) the patient had a history of myocardial infarction; (*b*) the patient had angina pectoris by the Rose questionnaire,[16] or (*c*) ischaemic changes were seen in the resting electrocardiogram (Minnesota codes 1·1–1·3, 4·1–4·3, 5·1–5·3, or 7·1 (Whitehall criteria)), including Q–QS abnormalities, ST segment depressions, T wave changes, or left bundle branch block.[17] A patient was considered to have hypertension if the systolic blood pressure was $\geqslant 160$ mm Hg or the diastolic blood pressure was $\geqslant 95$ mm Hg during supine rest or if the patient had been receiving drug treatment for hypertension.

Echocardiography

M mode echocardiography was performed with a sector electronic scanning type ultrasound diagnostic system (Toshiba (Sonolayer Model SSH-40A, Japan) and a 2·4 MHz transducer (Toshiba PSA-24B, Japan). Subjects were examined in the left lateral decubitus position. Cross sectional scans were used to position the M mode recordings just below the edge of the anterior mitral leaflet. M mode echocardiograms were recorded on photosensitive paper at a paper speed of 100 mm/s. Measurements were made from the paper recordings according to the recommendations of the American Society of Echocardiography[18] with a x-y digitiser (resolution 0·1 mm) interfaced to a computer.[19] Five consecutive or near consecutive cardiac cycles were measured and the means of the values were recorded. Echocardiographic measurements were carried out on all study subjects by the same investigator (JR). The following variables were recorded: diameter of the left atrium, left ventricular end diastolic diameter, and left ventricular end systolic diameter. Fractional shortening and peak rate of increase in left ventricular diameter during diastole (used as an index of left ventricular relaxation) were calculated by the computer.

Exercise testing

A bicycle ergometer exercise test with non-invasive gas exchange analysis was carried out on those patients who did not have dyspnoea at rest. The exercise test was performed by patients sitting on an electrically braked bicycle ergometer. The workload was continuously increased by 15 W every minute until the patient became exhausted. The rate of oxygen consumption was determined by analysing the expired gas breath by breath during exercise. A Medical Graphics Corporation CAD/Net system 2001 analyser was used in the analysis.[20] The average rate of oxygen consumption during the last 20 seconds of exercise was taken as peak oxygen consumption.

Hormone assays

Blood samples for homone analyses were taken in the early morning hours after an overnight

fast. A Teflon cannula (Venflon 18 G/1·2 mm, Sweden) was positioned in a large antebrachial vein, and patients rested in the supine position for at least 30 minutes. Blood was then drawn into prechilled EDTA tubes placed on ice. Plasma was separated at 4°C within 20 minutes, frozen immediately, and stored at −70°C until assay.

Radioimmunoassay techniques were used to measure plasma atrial natriuretic peptide concentration and renin activity as previously described.[1 21] Plasma aldosterone was measured by a commercial radioimmunoassay kit (Abbott Laboratories, Chicago, Illinois). Plasma concentrations of adrenaline and noradrenaline were assessed by high performance liquid chromatography with electrochemical detection.[22] The investigators in charge of hormone assessments (IT and FF) were not aware of the clinical condition of the individuals studied.

Statistical analysis

Results are expressed as means (SEM) and medians. SPSS programmes (Statistical Package for the Social Sciences, Chicago, USA) were used for statistical analyses. One way analysis of variance was used to detect overall differences between group means of normally distributed variables. If p value was $\leq 0{\cdot}05$ in one way analysis of variance, Student's *t* test for unpaired data was used in further comparisons. Hormone values showed a skewed distribution, and therefore the non-parametric Mann-Whitney test was used to compare hormone values. Frequency differences were tested by the χ^2 test. p Values of $<0{\cdot}05$ were regarded as significant. Correlation analyses were carried out by standard linear regression techniques available in the SPSS programmes; correlations were considered significant at $p < 0{\cdot}01$.

Results

CLINICAL CHARACTERISTICS

Most patients were in New York Heart Association functional class I–III, and thus symptoms suggestive of heart failure were in general mild or moderate (table 1). However, 10 patients (53%) in group 3 belonged to functional class IV. Twenty six patients (six men and 20 women) were classified "unlikely to have heart failure" (group 1). This shows that primary health care diagnosis of heart failure was more often incorrect in women than in men ($p < 0{\cdot}01$).[14] Obesity was common in all patient groups. There were signs of volume overload such as leg oedema, liver enlargement, or increased jugular venous pressure in four patients (15%) in group 1, six (40%) in group 2, and 13 (68%) in group 3.

Most patients had evidence of either coronary heart disease or hypertension and some were taking drugs for angina pectoris. According to the criteria used in this study, some of the control subjects also had hypertension as judged by a single blood pressure measurement. Coronary heart disease was more common in group 2 than in group 1. Hypertension was significantly more common in group 3 than in the control group or group 1, whereas no significant differences in frequencies of hyper-

Table 1 Some clinical characteristics, cardiac diseases, and use of cardiac drugs in control and patient groups

	Controls (n = 69)	*Group 1 (n = 26)*	*Group 2 (n = 15)*	*Group 3 (n = 19)*
Characteristics:				
Sex (male/female)	29/40	6/20	4/11	13/6‖
Age (yr)	61 (1)	59 (1)	63 (2)§	61 (2)
Heart rate (beats/min)	65 (1)	68 (2)	80 (6)‡	91 (4)‡§
Systolic blood pressure (mm Hg)	150 (3)	148 (4)	156 (8)	154 (6)
Diastolic blood pressure (mm Hg)	84 (1)	88 (1)	86 (3)*	90 (2)†
Weight (kg)	72 (2)	75 (1)	70 (2)	78 (3)
Body mass index (kg/m²)	26·2 (0·5)	29·3 (0·8)†	28·2 (1·6)	27·7 (1·2)
Relative heart volume (ml/m²)	430 (10)	420 (20)	550 (40)‡¶	670 (30)‡¶
NYHA class (n) (%):				
I		6 (23)		
II		15 (58)	7 (47)	3 (15)
III		4 (15)	7 (47)	6 (32)
IV		1 (4)	1 (6)	10 (53)
Cardiovascular disorders (n) (%):				
Coronary heart disease		15 (58)	9 (60)	16§ (80)
Hypertension	34 (42)	11 (42)	9 (60)	14*§ (70)
Valvar heart disease			2 (13)	2 (10)
Cardiac drugs (n) (%):				
β Blocker		4 (15)	2 (13)	6 (30)
Calcium antagonist			1 (7)	2 (10)
Long acting nitrate		3 (12)	2 (13)	4 (20)

Except where indicated data are given as mean (±SEM). NYHA class, New York Heart Association functional class. Hypertension was defined as a single casual blood pressure measurement ≥160/95 mm Hg. *p < 0·05, †p < 0·01, ‡p < 0·001, any patient group *v* control group; §p < 0·05, ‖p < 0·01, ¶p < 0·001, group 2 or 3 *v* group 1 (Student's *t* test or χ^2 test).

Table 2 Important biochemical variables (mean (SEM)) in control and patient groups

	Controls (n = 69)	*Group 1 (n = 26)*	*Group 2 (n = 15)*	*Group 3 (n = 19)*	*p Value*
Blood hematocrit	0·40 (0·0)	0·40 (0·01)	0·41 (0·01)	0·40 (0·01)	0·912
Serum ACE (μmol/min/l)	13·9 (0·5)	14·7 (0·9)	13·3 (1·0)	13·0 (1·1)	0·524
Serum albumin (g/l)	44 (0)	44 (1)	45 (1)	40 (1)†‡	0·001
Serum creatinine (μmol/l)	84 (1)	79 (2)	83 (3)	107 (7)†§	<0·001
Serum potassium (mmol/l)	4·3 (0·0)	4·2 (0·1)	4·3 (0·1)	4·4 (0·1)	0·241
Serum sodium (mmol/l)	145 (0)	145 (1)	145 (1)	143 (1)*	0·027

ACE, angiotensin converting enzyme. p Value by one way analysis of variance: *p < 0·05 and †p < 0·01 any patient group *v* control group; ‡p < 0·05, §p < 0·01, group 3 *v* group 1 (Student's *t* test).

Table 3 Echocardiographic variables and peak rate of oxygen consumption in the control group and patient groups (mean (SEM))

Variable	Control	n	Group 1	n	Group 2	n	Group 3	n	p Value
Fractional shortening (%)	34 (1)	63	33 (1)	23	28 (2)*§	13	21 (2)‡¶	17	<0·001
Left atrial diameter (mm)	33 (1)	63	35 (1)	23	36 (1)*	13	41 (1)‡¶	17	<0·001
LV end diastolic diameter (mm)	50 (1)	63	49 (1)	23	54 (1)*‖	13	59 (2)‡¶	17	<0·001
LV end systolic diameter (mm)	33 (1)	63	33 (1)	23	39 (2)†‖	13	45 (2)‡¶	17	<0·001
Peak rate of increase in LV diameter (cm/s)	12·2 (0·2)	60	10·8 (0·5)†	21	10·0 (1·0)*	13	8·0 (0·8)‡‖	16	<0·001
Peak $\dot{V}O_2$ (ml/kg/min)	26·0 (0·7)	69	20·7 (0·8)‡	23	16·9 (2·0)‡	13	14·9 (2·0)‡‖	7	<0·001

LV, left ventricular. $\dot{V}O_2$, rate of oxygen consumption. p Value by one way analysis of variance: *p < 0·05, †p < 0·01, ‡p < 0·001, groups 1–3 *v* control group; §p < 0·05, ‖p < 0·01, ¶p < 0·001, group 2 or 3 *v* group 1 (Student's *t* test).

Table 4 Comparison of plasma hormone values in control group and patient groups (mean (SEM) and medians (in parentheses))

	Control	n	Group 1	n	Group 2	n	Group 3	n
ANP (pg/ml)	51 (4) (50)	69	56 (6) (52)	26	130 (36)†§ (74)	15	267 (42)‡‖ (254)	19
Adrenaline (nmol/l)	0·30 (0·03) (0·24)	66	0·33 (0·04) (0·28)	25	0·51 (0·10)* (0·41)	14	0·41 (0·05)* (0·43)	17
Noradrenaline (nmol/l)	2·04 (0·10) (1·90)	66	2·12 (0·17) (1·86)	25	2·45 (0·29) (2·21)	14	2·63 (0·28)* (2·52)	17
Aldosterone (pmol/l)	130 (7) (120)	69	160 (15) (148)	26	146 (24) (137)	15	194 (132)* (162)	18
PRA (ng/ml/h)	2·7 (0·2) (2·3)	69	2·4 (0·2) (2·2)	26	3·3 (0·5) (2·7)	15	2·9 (0·6) (2·4)	19

ANP, atrial natriuretic peptide; PRA, plasma renin activity. *p < 0·05, †p < 0·01, ‡p < 0·001 for group 1, 2, or 3 *v* control groups; §p < 0·01, ‖p < 0·001, for group 2 or 3 *v* group 1 (Mann–Whitney non-parametric test).

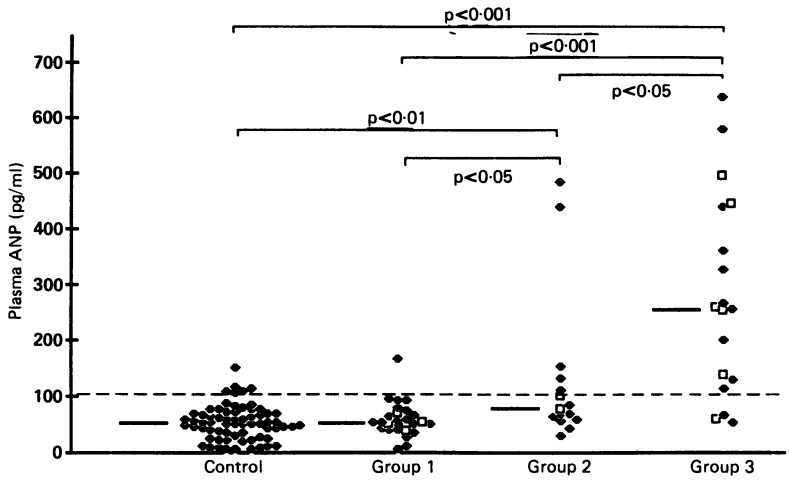

Figure 1 Plasma concentrations of atrial natriuretic peptide (ANP) in patients and controls. Group 1, heart failure unlikely; group 2, possible heart failure; and group 3, definite heart failure, according to the Boston classification. Open symbols indicate patients receiving β blockers. p Values indicate significance in the non-parametric test (Mann Whitney). Solid bars show medians; the dotted line represents the upper limit of the 95% confidence interval for values in the control group.

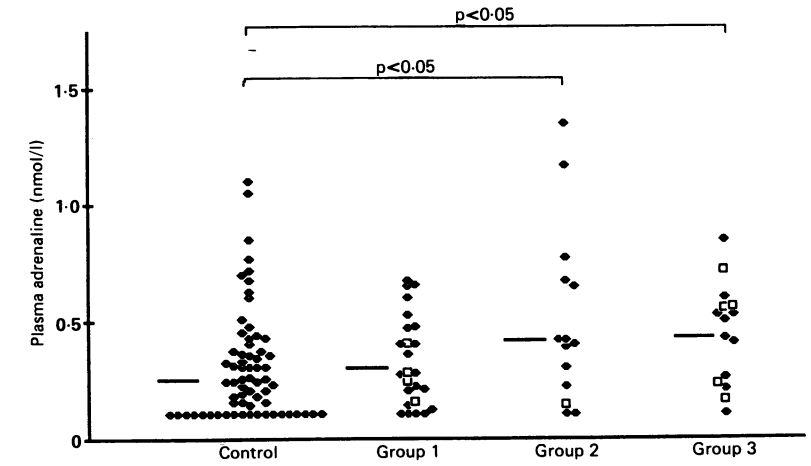

Figure 2 Plasma adrenaline concentrations in patients and controls (1 nmol/l = 183·2 pg/ml). See legend to figure 1 for an explanation of the groups and symbols.

tension were seen between group 1, group 2, and the control group. The serum creatinine concentration was higher in group 3 than in any other study group and serum sodium concentration was lower in group 3 than in the control group (table 2). In addition, the serum albumin concentration was lower in group 3 than in the control group or in group 1. No significant differences were seen in haematocrit between the study groups.

ECHOCARDIOGRAPHY AND EXERCISE TESTING

The left atrial and left ventricular diameters were greater and fractional shortening and peak rate of increase in left ventricular diameter were smaller in group 3 than in the control group or in group 1 (table 3). The dimensions of the cardiac chambers were greater and fractional shortening was smaller in group 2 than in the control group or in group 1. These data indicate that both left ventricular systolic and diastolic function were impaired in groups 2 and 3. There was no difference in indices of left ventricular systolic function between group 1 and the control group. On the other hand, the peak rate of increase in left ventricular dimension was lower in group 1 than in the control group, which suggests that left ventricular diastolic function was also impaired in group 1. Furthermore, the peak rate of oxygen consumption in the exercise test was greater in each patient group than in the control group and it was lower in group 3 than in group 1. The results of the echocardiographic and exercise measurements were essentially the same when men and women were analysed separately.

PLASMA HORMONES

Plasma atrial natriuretic peptide concentration was higher in group 3 than in any other study group and it was higher in group 2 than in the control group or group 1 (table 4, fig 1). Both plasma adrenaline and noradrenaline concentrations were somewhat higher in group 3 than

in the control group but they were not higher in group 3 than in group 1 or group 2 (figs 2 and 3). Plasma aldosterone concentration showed a wide range of variation in all study groups (fig 4). There was no significant difference between the study groups in plasma renin activity, which was considerably increased in only four patients (fig 5).

There were no significant differences in plasma hormone values between men and women, and no significant differences between non-obese and obese persons either in the entire patient population or within any of the study groups. The results were essentially the same when patients treated with β blockers, calcium antagonists, or long acting nitrates were excluded separately or altogether from the analysis. The results also remained unchanged when those controls who were defined as having hypertension were not included. Plasma atrial natriuretic peptide concentration was higher in patients who had signs of volume overload than in patients who had none of these signs (192 (23) pg/ml *v* 113 (35) pg/ml, $p < 0{\cdot}01$ (all patients included)). However, even when only those patients in whom no signs of volume overload were seen were included in the analysis, plasma atrial natriuretic peptide concentration was still higher in group 3 than in group 1 (297 (81) pg/ml *v* 53 (7) pg/ml, $p < 0{\cdot}01$). We found no significant differences between the study groups for any other hormones which are associated signs of volume overload.

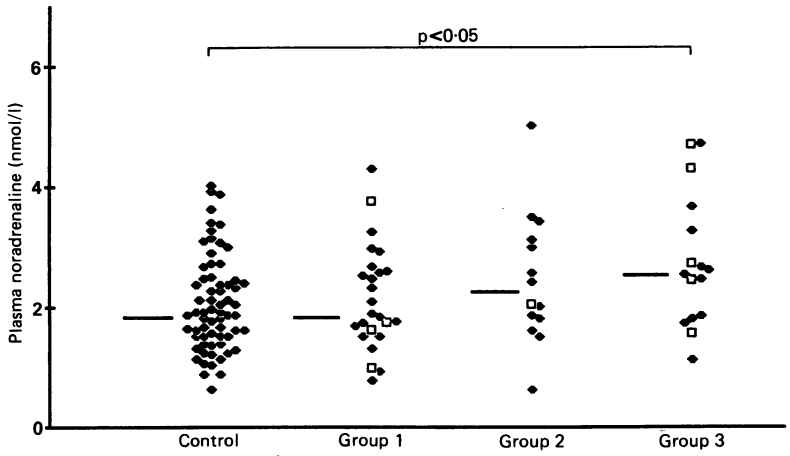

Figure 3 Plasma noradrenaline concentrations (1 nmol/l = 169·2 pg/ml) in patients and controls. See legend to fig 1 for an explanation of the groups and symbols.

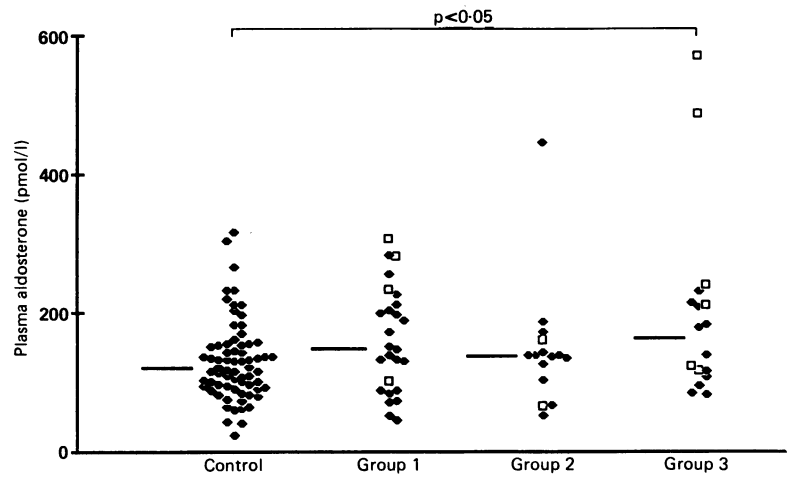

Figure 4 Plasma aldosterone concentrations in patients and controls subjects. See legend to fig 1 for an explanation of the groups and symbols.

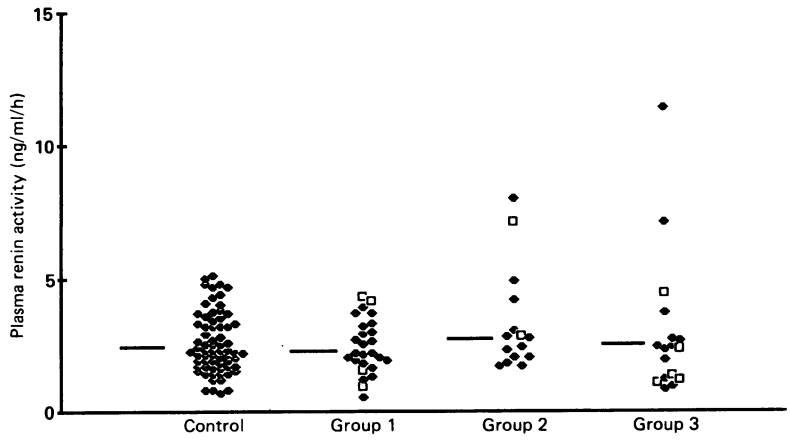

Figure 5 Plasma renin activities in patients and controls. See legend to fig 1 for an explanation of the groups and symbols.

Table 5 shows the correlations of plasma hormone values with each other and with some other selected variables. All patients were included in these linear regression analyses. There was a positive correlation between plasma atrial natriuretic peptide, adrenaline, and noradrenaline concentrations. Plasma atrial natriuretic peptide concentration was also correlated positively with heart rate, relative heart volume, New York Heart Association functional class, and with left atrial and ventricular dimensions determined by echocardiography. Plasma atrial natriuretic peptide concentration was negatively correlated with fractional shortening, peak rate of increase in left ventricular diameter, and peak rate of oxygen consumption.

In group 3, there was a statistically significant inverse correlation between plasma atrial natriuretic peptide concentration and peak rate of increase in left ventricular diameter ($r = -0{\cdot}603$, $p < 0{\cdot}01$) and with peak rate of oxygen consumption ($r = -0{\cdot}966$, $p < 0{\cdot}01$). No other significant correlations were found within this group between plasma hormone values and the variables listed in table 5. We found no significant correlations between any of the plasma hormone measurements in the controls, but there was a weak inverse correlation between plasma adrenaline concentration and left ventricular end diastolic and end systolic diameters ($r = -0{\cdot}287$, $p < 0{\cdot}01$ and $r = -0{\cdot}289$, $p < 0{\cdot}01$, respectively).

We assessed the possible usefulness of plasma atrial natriuretic peptide measurement as a diagnostic test in confirming the presence or absence of "definite heart failure" by the Boston classification by using the upper limit of the 95% confidence interval in the control group (101 pg/ml) as the cut off value. This cut-off value had a sensitivity of 83% and a specificity of 85% in identifying patients belonging to group 3—that is, patients with "definite heart failure" (fig 1). Furthermore, if the plasma concentration of atrial natriuretic peptide was above the cut off level, the probability that the patient belonged to group 3 was 71% (positive predictive value) and if the

Table 5 Correlation coefficients of hormone values with each other and with other selected variables, all patients included

Variable	*ANP*	*Adrenaline*	*Noradrenaline*	*Aldosterone*	*PRA*
ANP	1·000	0·361*	0·466†	0·149	0·190
Adrenaline	0·361*	1·000	0·393*	−0·090	−0·238
Noradrenaline	0·466†	0·393*	1·000	−0·262	−0·092
Aldosterone	0·149	−0·090	0·262	1·000	0·153
PRA	0·190	−0·238	−0·092	0·153	1·000
Heart rate	0·452†	0·183	0·242	0·054	0·118
Relative heart volume	0·616†	0·274	0·321	0·128	0·073
NYHA class	0·500†	0·136	0·124	0·138	0·140
Fractional shortening	−0·580†	−0·230	−0·288	−0·069	0·304
Left atrial dimension	0·341*	0·016	0·095	−0·113	0·009
LV end diastolic diameter	0·481†	−0·073	0·026	0·286	0·099
LV end systolic diameter	0·581†	0·080	0·141	0·080	0·240
Peak rate of increase in LV diameter	−0·448*	−0·093	−0·174	0·056	−0·337
Peak rate of oxygen consumption	−0·469*	−0·152	−0·339	−0·330	−0·244

ANP, atrial natriuretic peptide; LV, left ventricular; NYHA class, New York Heart Association functional class; PRA, plasma renin activity. Correlation coefficients were obtained by linear regression analysis; *$p < 0·01$, †$p < 0·001$.

plasma atrial natriuretic peptide concentration was equal to or below the cut off level, the probability that the patient did not belong to group 3 was 92% (negative predictive value). Three patients who had been classified as group 3 had plasma atrial natriuretic peptide concentrations below 101 pg/ml (fig 1), but two of them had been receiving treatment with calcium antagonists and one with long acting nitrates. On the other hand, two patients belonging to group 2 had plasma atrial natriuretic peptide concentrations considerably above the cut off value; one had aortic valve stenosis and incompetence and the other had aortic valve incompetence. Just one of 21 patients with plasma atrial natriuretic peptide of > 101 pg/ml was classified as group 1 and that patient had atrial fibrillation.

Discussion

This study on the neuroendocrine activation in newly diagnosed heart failure showed that the concentration of plasma atrial natriuretic peptide was raised and sympathetic nervous activity was already increased before the start of treatment, whereas the renin-angiotensin-aldosterone system was not activated at this stage.

Since the discovery of atrial natriuretic peptide by deBold *et al*,[23] the peptide has been a subject of intensive research. It is now well known that atrial natriuretic peptide is stored in both the atrial and ventricular cardiocytes[24 25] and is released from the cardiocytes in response to stretching of the atrial tissue,[26 27] expansion of circulating blood volume,[28] or increased atrial contraction frequency.[29] Previous studies have shown, furthermore, that the plasma concentration of atrial natriuretic peptide is raised in patients with chronic heart failure (during drug treatment), and that the rise is proportional to the increase in atrial pressure.[3] In our study the plasma atrial natriuretic peptide concentration was raised in all patients with definite heart failure who were not treated with vasodilators. Furthermore, in our untreated patients the plasma concentration of atrial natriuretic peptide correlated with the severity of dyspnoea, with peak oxygen consumption, with radiographic heart volume, and with echocardiographic indicators of the severity of left ventricular dysfunction. Although no haemodynamic data were available on our patients with heart failure, increased atrial pressure (or stretch) is the most likely mechanism underlying the raised plasma atrial natriuretic peptide concentration.

Several studies have shown that sympathetic nervous activity, as judged by measurement of plasma noradrenaline concentration, is increased in patients with heart failure during treatment with diuretics.[30–32] However, studies of sympathetic nervous activity in untreated heart failure have been contradictory. In a recent study, plasma noradrenaline concentration was not raised in patients with mild heart failure from whom cardiac medication had been withdrawn one week before the study.[10] Whereas plasma noradrenaline concentrations were raised in untreated patients with moderately severe[9] or severe heart failure[12] and also in patients with asymptomatic left ventricular dysfunction.[33] In our study, plasma adrenaline and noradrenaline concentrations were both significantly higher in patients with "definite" heart failure than in healthy controls. Thus our results accord with activation of the sympathetic nervous system early in the natural course of heart failure.

It is generally accepted that the activity of the renin-angiotensin-aldosterone system is increased in patients with advanced chronic heart failure treated with diuretics.[34 35] On the other hand, some previous studies based on small series of patients suggested that the renin angiotensin-aldosterone system would not be activated in patients with heart failure who have not received treatment with diuretics.[11 12 14] The results of the present study confirm that activation of this system is uncommon in untreated heart failure. However, because these findings apply to the activity of the renin-angiotensin-aldosterone system in circulating blood only they do not exclude the possibility that the tissue renin-angiotensin systems could be altered in heart failure.

We found that plasma atrial natriuretic peptide concentration was higher in those patients in whom there was a definite diagnosis of heart failure according to the Boston classification and that it was uncommon in patients who proved not to be in heart failure. We are cautious about drawing definite conclusions from this cross sectional study, but our findings do suggest that the measurement of plasma

atrial natriuretic peptide might be helpful in the diagnostic evaluation of patients with suspected heart failure and that this measurement could be particularly useful in excluding heart failure.

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