How does treatment influence endocrine mechanisms in acute severe heart failure? Effects on cardiac natriuretic peptides, the renin system, neuropeptide Y and catecholamines

Constantinos G. MISSOURIS*, Eric GROUZMANN†, Martin G. BUCKLEY‡§, Jeffrey BARRON∥, Graham A. MACGREGOR∥ and Donald R. J. SINGER¶
*Department of Cardiology, St George's Hospital Medical School, Cranmer Terrace, London SW 17 ORE, U.K., †Blood Pressure Unit, St George's Hospital Medical School, Cranmer Terrace, London SW 17 ORE, U.K., ‡Clinical Pharmacology Unit, Department of Pharmacology and Clinical Pharmacology, St George's Hospital Medical School, Cranmer Terrace, London SW 17 ORE, U.K., ∥Division d'Hypertension, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, §Imperial College National Heart and Lung Institute Heart Science Centre, Harefield UB9 6JH, U.K., and ¶Department of Chemical Pathology, St Helier Hospital, Carshalton, Surrey

1. Hormones involved in cardiovascular regulation are influenced by drug treatment. It is therefore difficult to study endocrine mechanisms in heart failure as most patients are already on treatment by the time they reach hospital.

2. We studied nine hospital in-patients before and after treatment of acute New York Heart Association class IV heart failure.

3. Before treatment, plasma brain and atrial natriuretic peptides were markedly elevated (BNP 121 ± 26 pg/ml, ANP 163 ± 33 pg/ml; normal range: BNP 3.9 ± 0.3 pg/ml, ANP 8.6 ± 0.8 pg/ml) and correlated positively with serum creatinine and left ventricular end-diastolic diameter and negatively with ejection fraction. Eight patients improved and one died.

4. With improvement plasma ANP and BNP fell. Initial renin activity was within the normal range but increased on treatment. Plasma neuropeptide Y and adrenaline remained normal before and after treatment in the eight patients who improved. Initial plasma noradrenaline was in the normal range in four of these patients and just above normal in a further four. In the patient who died, initial plasma neuropeptide Y and catecholamines were very high.

5. Plasma BNP emerged as complementary to ANP as a dynamic index in severe heart failure; however, renal function is also an important determinant of plasma BNP and ANP. There is little evidence for activation of the circulating renin-angiotensin-aldosterone system or neuropeptide Y before treatment of acute heart failure.

INTRODUCTION

Heart failure is a complex syndrome in which a primary disturbance of cardiac contraction leads to retention of sodium and water by the kidney and compensatory activation of endocrine and neural reflexes that affect the myocardium [1]. The cardiac hormone, atrial natriuretic peptide (ANP), has an important role in regulation of blood volume and is predominantly secreted by the atria with recruitment of ventricular synthesis in heart failure [2]. In contrast, brain natriuretic peptide (BNP) has been shown to be synthesized in the human heart in the atria and in the ventricles in normal physiology [3]. BNP is responsive to changes in blood volume, plasma BNP levels increasing with dietary sodium loading in normal subjects [4], and decreasing with reductions in blood volume associated with haemodialysis [5]. Plasma BNP is increased in essential hypertension [5] and increases in proportion to the severity of heart failure [3]. When infused in pharmacological amounts BNP has significant haemodynamic effects on blood pressure, pulmonary capillary wedge pressure and systemic vascular resistance, as well as reducing aldosterone levels [6]. These peptides may therefore be important in the pathophysiology of heart failure. In addition there is a great interest in the value of measuring these peptides as indices of cardiac dysfunction [7–10]. Many studies have shown that plasma ANP levels are elevated in proportion to the severity of heart failure. It is also well established that plasma ANP is a sensitive index of response to treatment [11]. As BNP is predominantly secreted from the atrium while there has been speculation that the measurement of plasma BNP may be a better index of ventricular dysfunction than ANP.

There is continuing controversy as to the role of the renin-angiotensin system with evidence that in mild heart failure there is no stimulation of the system but a view that in patients with more severe heart failure it may well play a role [12,13]. There is also controversy about the levels of circulating neuropeptide Y (NPY)
and catecholamines in congestive heart failure and about the potential confusing effect of drug treatment on the activity of the sympathetic nervous system in these patients [14].

As many hormones involved in cardiovascular regulation are influenced by drug treatment, it is difficult to study endocrine mechanisms in chronic heart failure as most patients are already on treatment by the time they reach hospital. We therefore assessed endocrine mechanisms in patients admitted to hospital with untreated acute severe heart failure.

In particular, we examined whether measurement of plasma BNP may be a useful index of severity of heart failure. In an attempt to resolve some of the controversy about activation of other endocrine mechanisms in heart failure, we also studied the circulating renin–angiotensin system, NPY and catecholamine levels in patients with severe but untreated heart failure.

**PATIENTS AND METHODS**

Nine subjects [eight male, mean age 70 (57–86) years] with untreated acute severe heart failure were studied as hospital in-patients in South London. All patients gave informed consent for the investigations which were approved by the local hospital ethics committee. The investigation conforms with the principles outlined in the Declaration of Helsinki (1989) of the World Medical Association.

Patients were assessed for the clinical severity of heart failure on admission and before discharge from hospital by a single physician, using the New York Heart Association (NYHA) classification. Supine blood pressure was recorded three times, 2 min apart, using a semi-automated ultrasound sphygmomanometer (Arteriosonde, Roche). Blood samples for hormone measurements were spun immediately at 4 °C and plasma stored at −20 °C until assay. Plasma renin activity (PRA), aldosterone, ANP and BNP were measured by RIA [5,15]. Plasma NPY was measured using an amplified enzyme immunoassay and noradrenaline and adrenaline by HPLC with electrochemical detection [16,17]. Twenty-four-hour urine samples were collected for measurement of sodium and creatinine excretion.

An echocardiogram was performed with a 2.5 MHz transducer (Hewlett Packard-mode 1000c) to look at left ventricular function and indices before treatment was started. After treatment patients were studied again with echocardiography. Short axis views, with the patient in the left lateral position, were obtained using standard parasternal windows. Echograms were read by an independent observer blinded to the clinical details of the patients. Measurements of the interventricular septal thickness, posterior wall thickness and left ventricular diameter in systole and diastole were made according to the American Society of Echocardiography leading edge convention. The left ventricular ejection fraction was calculated from the cube of the ventricular dimensions at end-systole and end-diastole [18].

After initial clinical assessment, blood sampling and echocardiography, all patients received intravenous frusemide. In addition, four patients were treated with an angiotensin-converting enzyme (ACE) inhibitor. Treatment was under the care of the admitting physician.

**STATISTICAL ANALYSIS**

Results are given as means ± S.E.M. Paired measurements were compared using the Wilcoxon sign rank sum test. Associations between hormones and other variables were tested using linear regression statistics, or in the case of non-parametric data using Spearman correlation analysis. A P value of < 0.05 was considered statistically significant.

**RESULTS**

The clinical and hormonal indices in patients with acute severe heart failure are summarized in Tables 1 and 2 respectively.

Clinical characteristics and outcome

Seven patients had ischaemic heart disease and two had valvular heart disease. Before acute exacerbation of symptoms leading to admission two patients were in NYHA class II and seven in class III. On admission, all were short of breath at rest and in NYHA class IV. None of the patients was in atrial fibrillation or had primary rhythm disturbance. All patients had pulmonary venous hypertension and cardiomegaly on chest radiograph. Three had possible evidence of acute myocardial infarction based on enzyme changes alone. In seven patients, good quality echograms showing continuous echoes of the interventricular septum and left ventricular posterior wall were obtained and were included in the final analysis. Five of these had low ejection fraction. However, the two patients with mitral regurgitation had an ejection fraction at the lower end of the normal range. In these patients the ejection fraction in isolation appeared to be a poor estimate of left ventricular function. Eight patients improved with treatment and were discharged. One patient deteriorated and died on day 6 of the study. Table 3 outlines the individual characteristics of all nine patients.

Plasma BNP and ANP

**Results on admission before drug treatment.** On admission, before any treatment was given, plasma levels of both BNP and ANP were markedly elevated in all patients (normal range: BNP 3.9 ± 0.3 pg/ml, ANP 8.6 ± 0.8 pg/ml). The mean values of BNP and ANP were 106 ± 25 pg/ml and 136 ± 26 pg/ml respectively in the eight patients whose heart failure improved...
Table I  Changes in clinical, echocardiographic, biochemical and haematological indices with treatment in nine patients with moderate to severe heart failure

<table>
<thead>
<tr>
<th>NYHA class improvement</th>
<th>NYHA class deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Before treatment</td>
</tr>
<tr>
<td></td>
<td>(n = 8)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>68.9±4.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68.9 ± 5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>Supine blood pressure (mmHg)</td>
<td>148 ± 11</td>
</tr>
<tr>
<td>Left ventricular diameter, diastole (cm)</td>
<td>6.2 ± 0.4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>183 ± 55</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.8 ± 0.9</td>
</tr>
<tr>
<td>Packed cell volume ratio</td>
<td>0.352 ± 0.02</td>
</tr>
</tbody>
</table>

Table II  Changes in plasma hormonal values with treatment in nine patients with moderate to severe heart failure

<table>
<thead>
<tr>
<th>NYHA class improvement</th>
<th>NYHA class deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma BNP (pg/ml)</td>
<td>Before treatment</td>
</tr>
<tr>
<td></td>
<td>(n = 8)</td>
</tr>
<tr>
<td>Plasma ANP (pg/ml)</td>
<td>106 ± 25</td>
</tr>
<tr>
<td>PRA (nmol ANG I·h⁻¹·l⁻¹)</td>
<td>136 ± 76</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/l)</td>
<td>0.92 ± 0.23</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/l)</td>
<td>278 ± 45</td>
</tr>
<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>1.95 ± 0.69</td>
</tr>
<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>5.5 ± 0.66</td>
</tr>
<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>0.34 ± 0.07</td>
</tr>
</tbody>
</table>

Table III  Individual characteristics of nine patients with acute severe heart failure

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Ejection fraction (%) by echocardiography</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>27</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>38</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>M</td>
<td>44</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>M</td>
<td>54</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>5</td>
<td>82</td>
<td>M</td>
<td>21</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>M</td>
<td>-</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>F</td>
<td>-</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>F</td>
<td>56</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>42</td>
<td>Ischaemic heart disease</td>
</tr>
</tbody>
</table>

Hormones in untreated severe heart failure

Results after treatment. In those patients whose
Plasma renin activity decreased significantly with treatment from 17.1 ± 1 ng/ml/hr to 10.1 ± 1 ng/ml/hr (P < 0.025). Changes in plasma ANP reflected clinical outcome in all nine patients. In the eight patients who improved, plasma ANP decreased. However, although average BNP levels also decreased with treatment, changes in individual patients were more variable. Changes in plasma BNP were related to clinical outcome in only seven patients. The relationship between left ventricular end-diastolic diameter and both plasma ANP and BNP after treatment appeared to be similar (results not shown).

Table 4 summarizes hormonal measurements before and after treatment in those subjects treated with an ACE inhibitor compared with those receiving other treatment. In both groups, ANP and BNP decreased with treatment. PRA was in the normal range in both groups before treatment and then increased with treatment in both groups, more so in those given an ACE inhibitor. As expected, aldosterone remained suppressed in those given an ACE inhibitor but increased with diuretic treatment in the absence of ACE inhibition.

**PRA**

PRA before treatment was at the lower end of the normal range in all subjects with acute severe heart failure (normal range 0.38–1.92 nmol ANG 1·h⁻¹·l⁻¹). In those patients whose heart failure improved, mean PRA was 0.92 ± 0.23 nmol ANG 1·h⁻¹·l⁻¹ and increased with treatment to 4.08 ± 1.69 nmol ANG 1·h⁻¹·l⁻¹ (Wilcoxon: P < 0.012; Figure 2). In the patient who died, PRA also increased. Thus, changes in PRA appeared to reflect treatment rather than clinical outcome.

**Plasma aldosterone**

Plasma aldosterone before treatment was normal in all eight patients whose heart failure improved, with a
Hormones in untreated severe heart failure

Plasma NPY

On admission, before treatment was given, plasma levels of NPY were within normal limits at 1.95 ± 0.69 pmol/l (normal range < 7.5 pmol/l) in the eight patients whose heart failure improved. In these eight patients, plasma NPY did not change significantly with treatment (1.92 ± 0.72 pmol/l; P = 0.67). In the patient who died, the basal plasma NPY level was very high (50.0 pmol/l) and remained elevated (9.6 pmol/l) despite treatment (Table 2). Basal plasma NPY in all nine patients correlated better with plasma noradrenaline (P = 0.08) than with adrenaline (P = 0.72), although none of these associations reached statistical significance. No significant association was found between plasma NPY and either left ventricular end-diastolic diameter or ejection fraction (P = 0.29 and P = 0.37 respectively). Furthermore, there was no clear relationship between changes in plasma NPY levels and clinical outcome as assessed by changes in NYHA class (Figure 3).

Plasma catecholamines

Pretreatment levels of mean plasma noradrenaline were slightly raised to 5.5 ± 0.6 nmol/l (normal range 0–5 nmol/l) in the eight patients whose heart failure improved, and decreased with treatment to 4.2 ± 0.3 nmol/l (P = 0.07). In contrast, mean basal adrenaline in these eight patients was normal at 0.34 ± 0.07 nmol/l (normal range 0–1.0 nmol/l) and also decreased with treatment to 0.28 ± 0.12 nmol/l (P = 0.21). In the patient who died, basal plasma catecholamines were very high (noradrenaline, 12.9 nmol/l; adrenaline, 3.1 nmol/l) and did not return to normal levels with treatment. However, there was no consistent relationship between changes in plasma noradrenaline or adrenaline (Figure 4) and clinical outcome as assessed by changes in NYHA class.

Other measurements in patients with acute or chronic heart failure

Our subjects were elderly and urinary collections likely to have been incomplete, as assessed from the urinary creatinine values (initial: 10.9 ± 3.0 mmol/l; final 6.4 ± 1.9 mmol/l). The initial 24 h urine collection gave high values for sodium excretion, reflecting a combination of sodium intake and the response to initial diuretic treatment (249 ± 62 mmol/24 h). The 24 h urinary sodium results on discharge normalized to the admission creatinine excretion gave average values typical for sodium intake in our local population (uncorrected: 91 ± 36 mmol/24 h; corrected for urinary creatinine excretion: 157 ± 59 mmol/24 h). These results suggest that a decrease in dietary sodium excretion was unlikely to be the major mechanism for the changes in BNP, ANP or PRA expression which we observed. In the eight patients in whom heart failure improved, supine blood pressure, heart rate and body weight decreased with treatment while left ventricular ejection fraction, serum creatinine, haemoglobin and packed cell volume increased (Table 1).
DISCUSSION

This is the first detailed report in which a wide range of important cardiovascular regulatory hormones have been measured in subjects presenting with acute severe heart failure from whom blood samples have been taken before administration of drug treatment.

Plasma BNP and ANP

In our study in patients with untreated acute severe heart failure the most striking hormonal abnormalities were the very high levels of both plasma BNP and ANP. Mechanisms of BNP release are not fully understood. The degree of renal impairment, as assessed by serum creatinine, was positively correlated with both BNP and ANP, suggesting that reduced renal clearance is a further cause of the raised levels of these hormones found in patients with heart failure. Our results show that in this setting another possible mechanism regulating BNP secretion is an increase in left ventricular end-diastolic diameter. From the present study we cannot differentiate between increased stretch and increased pressure as the mechanism responsible. Further support for this mechanism comes from the strong negative correlation between plasma BNP and left ventricular ejection fraction assessed by echocardiography. There are limitations to the interpretation of echocardiographic data, particularly in patients with ischaemic heart disease who may have regional wall abnormalities. However, more sophisticated measurements are difficult in ill patients. With these limitations we feel, nonetheless, that our observations are of interest. Furthermore, our findings are consistent with a reported negative correlation between BNP and radionuclide ejection fraction in patients recovering from anterior myocardial infarction [7].

A further important finding was that plasma BNP, like ANP, is an index of the response to treatment of severe heart failure. There have been no reports previously published of the changes in plasma BNP with clinical improvement of severe heart failure which have not been confounded by previous treatment. However, although the average changes in plasma BNP and ANP with treatment were similar, plasma BNP appeared to be a less consistent index of response to treatment than plasma ANP. Changes in plasma ANP predicted clinical improvement or deterioration in all nine patients but in only seven out of nine for changes in BNP.

PRA

Diuretics, which are standard first-line treatment for heart failure, are well recognized to stimulate the renin–angiotensin–aldosterone system [19]. ACE inhibitors, on the other hand, inhibit the activity of converting enzyme, preventing increases in angiotensin and aldosterone with a resulting reflex increase in PRA. This has contributed to controversy about the role of the renin–angiotensin system in patients with heart failure, as many studies have been confounded by stimulation of this system by drug treatment already present when initial measurements were obtained [20]. In all our untreated patients with heart failure, PRA was initially in the normal range, increasing only when treatment was given. This observation is consistent with the findings of Anand et al. [21] in a study of five initially untreated patients, and Bayliss et al. [12] reported normal values for PRA in patients with untreated heart failure that was mild enough to allow them to perform maximal exercise on the treadmill. Although data from a cross-sectional study by Anand et al. [19] of untreated patients in India showed raised PRA in some patients with heart failure, the PRA was well within the normal range in three of the five patients with NYHA class IV disease. Furthermore, in a recent study, the same group now reports activity of the renin–angiotensin system to be within the normal range in nine patients with untreated severe heart failure [22]. Taken together with these previous reports, our study strongly suggests that activation of the renin–angiotensin system is not a major feature of severe heart failure, in the absence of treatment. The raised levels of ANP noted in this and in previous studies of heart failure may be relevant to the above observations that PRA is rarely elevated in untreated heart failure: high levels of ANP can inhibit secretion of renin from the kidney [23]. There are several studies showing that either exogenous or endogenous increases in plasma ANP in patients with heart failure have effects which tend to counteract the above effects of the renin system. Secondly, potentiation of endogenous ANP using neutral endopeptidase inhibitors has similar effects [24].

Plasma aldosterone

Our data also demonstrate that plasma aldosterone is usually normal in patients with acute severe heart failure, increasing above the normal range only with treatment. Normal values of plasma aldosterone have also been reported in patients with mild heart failure [12]. Studies in animals and man suggest that plasma aldosterone levels may be reduced by a direct inhibitory effect of ANP on the zona glomerulosa of the adrenal gland and indirectly by reduction of plasma angiotensin II levels [25]. Thus plasma ANP may have an important role in the pathophysiology of heart failure by counterbalancing the vasoconstrictor and salt-retaining properties of the renin–angiotensin–aldosterone system. In view of its similar biological activity to ANP [6] it is likely that elevated BNP levels may have comparable pathophysiological effects in heart failure.

Plasma NPY

NPY is co-localized and co-released with noradrenaline in peripheral and central neurons including
nerves within the myocardium and around cardiac blood vessels [26]. With handgrip and orthostatic stress, the increase in NPY is less pronounced than that of catecholamines and levels of NPY may even paradoxically decrease [27]; thus release of NPY and catecholamines is not invariably linked. NPY has vasoconstrictor effects on animal and human coronary arteries [28,29] and negative inotropic and chronotropic effects [30]. Increased secretion may thus have deleterious effects on ventricular function in patients with congestive heart failure.

However, in our study, all but one patient with severe heart failure had normal plasma levels of NPY, when measured before treatment was started. Furthermore, for all the patients in whom heart failure improved, there was no significant change in NPY levels with treatment. In the patient whose clinical condition deteriorated, baseline plasma NPY was very high and remained elevated despite treatment.

Previous authors have reported raised NPY values in heart failure [14,31]. However, the above studies have the following limitations: firstly, at entry, all patients were being treated with diuretics or vasoactive drugs which may have influenced the results, and secondly the polyclonal antibodies used in the RIA lacked specificity.

In the present study, patients with acute severe heart failure were investigated who had never received previous treatment, thus avoiding potential effects of drug treatment on plasma NPY levels. Secondly, we used a two-site, sandwich amplified enzyme immunoassay which recognizes the entire amidated form of NPY known to be biologically active [16]. This assay has a high sensitivity and specificity because of the use of two high-affinity anti-NPY monoclonal antibodies which do not cross-react with other NPY-like peptides such as the pancreatic polypeptide Y or peptide YY. Our results are in agreement with those of Dubois-Rande et al. [32] who used a similar assay and found no difference in the levels of NPY between control subjects and patients with congestive heart failure off treatment for 48 h. Recently, normal plasma NPY levels were also reported in treated patients with mild heart failure [33]. Thus our study, along with these two reports, suggests that the increased levels of plasma NPY reported in heart failure may largely reflect the lack of specificity of previous polyclonal antibody assays [32,33].

Plasma catecholamines

In our study we demonstrated that plasma noradrenaline but not adrenaline was mildly elevated in 4 out of 9 patients with untreated heart failure. However, in the patient who deteriorated and died, pretreatment plasma catecholamine levels were very high and did not return to normal with treatment.

In order to evaluate critically the relationship between sympathetic output and circulating noradrenaline, 'spillover' from the synaptic cleft into the circulation must be considered [34]. The plasma concentration of this neurotransmitter is determined largely from noradrenaline released by sympathetic nerves with only a small contribution from the adrenal medulla [35]. It is now generally agreed that the increase in plasma noradrenaline concentration in response to physiological stimuli appears to relate to the degree of sympathetic nervous system activity [36-38].

The role of the sympathetic nervous system in heart failure is controversial. The SOLVD investigators reported mild activation of the sympathetic nervous system early on in patients with left ventricular systolic dysfunction [39]. Furthermore, some studies, including those using noradrenaline turnover analysis or microneurography, have reported that the sympathetic nervous system is activated in heart failure [14]. Treatment may have confounded some of these studies. Patients were only off treatment for 18 h before intraneural recordings [40] and for 5 days before noradrenaline turnover studies [41]. The heightened adrenergic stimulation may initially help to maintain cardiac output but could ultimately contribute to the deterioration in cardiac function [42]. Evidence for such a role is provided by the observation of a marked depletion of tissue noradrenaline levels and β1 adrenergic receptors in patients with idiopathic dilated cardiomyopathy or isolated right heart failure [43]. In support of increased sympathetic nervous system release of NPY in heart failure, Bristow et al. [43] reported a marked depletion of tissue NPY levels in failing ventricles from patients with idiopathic dilated cardiomyopathy. Furthermore, there are clear clinical examples of conditions in which catecholamines may be contributing to cardiac disease. The association between elevated plasma levels of noradrenaline and adrenaline in patients with neuroendocrine tumours, such as phaeochromocytomas, and dilated cardiomyopathy is well recognized [44]. Furthermore, the dilated cardiomyopathy in these patients is reversible after removal of the catecholamine-secreting tumour.

Our results and those of others suggest that, even in acute severe heart failure, in the absence of treatment, plasma noradrenaline may be only mildly raised, while adrenaline is not elevated [12]. Nonetheless, high plasma noradrenaline levels have been linked to poor prognosis in patients with chronic heart failure [45].

Blood pressure, heart failure and hormones

The average blood pressure values in our subjects when admitted with severe heart failure before treatment were within the range for mild systolic hypertension. These levels, in fact, are comparable or lower than in subjects of similar age in the general population without heart failure. Nonetheless, mild systolic hypertension is typical of many patients with heart failure and, for example, in the SHEP study [46] admissions to hospital because of heart failure were much more common in untreated patients than in those who had the benefit of anti-hypertensive drugs.
In addition, in the large studies of ACE inhibitors as treatment for heart failure, preceding hypertension was recognized to be an important risk factor in 20–40% of subjects. Our study is thus of interest in including patients with the usual background of risk factors for heart failure seen in other studies.

It is clearly possible that the mildly raised blood pressure in some of these patients could have contributed in part to the raised levels of cardiac peptides [24]. However, the 15–25-fold increase in levels of cardiac peptides in the present study was greatly in excess of the usual 2–3-fold elevation of these peptides attributable to raised blood pressure alone [24].

Conclusions

This study gives important insight into hormonal mechanisms in acute, severe heart failure without the confounding influence of drug treatment. Our results suggest that ventricular haemodynamics and renal function are important determinants of plasma BNP and ANP levels in untreated patients. They also provide little evidence for activation of the circulating renin–angiotensin–aldosterone system or the neurohormones, NPY and catecholamines, in these patients before treatment is given. In the treatment part of our study, plasma BNP emerged as a dynamic index of acute changes in left ventricular function and thus possibly of short-term outcome in heart failure. This complements recent reports suggesting that plasma BNP may be a useful long-term prognostic marker of severity and survival in patients with acute myocardial infarction [8,9] or pulmonary hypertension [10]. Our study also suggests, as in previous reports in patients with milder heart failure, that the main reason for activation of the renin–angiotensin–aldosterone system in severe heart failure is drug treatment.

Acknowledgments

We thank Alison Blackwood BSc and Michelle Miller BSc for measurements of PRA and aldosterone, and Nirmala Markandu SRN and Christine Carney SRN for their hard work with the patients. C.G.M., G.A.M. and D.R.J.S. are members of the St George's Cardiovascular Research Group.

References

Hormones in untreated severe heart failure


Received 20 October 1997; accepted 28 January 1998.