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Neurohormonal activation in patients with mild or moderately severe congestive heart failure and effects of ramipril

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Abstract

***Objectives*—To describe neurohormonal activation in patients with mild or moderate heart failure and how it may be modified by treatment with ramipril.**

***Setting*—Cardiology departments at 24 hospitals in Denmark, Finland, Norway, and Sweden.**

***Patients*—223 patients with mild or moderately severe congestive heart failure who were taking diuretics with or without digitalis.**

***Design*—Randomised, double bind, multicentre, placebo controlled comparison of ramipril and placebo. Venous blood samples were drawn at rest, before blind treatment, and after 12 weeks of treatment with the study drug. A probability prediction score for mortality derived by stepwise linear discriminant from neurohormone data in the first cooperative north Scandinavian enalapril survival study (CONSENSUS I) was used to assess combined activity of the different neurohormonal systems.**

***Results*—Plasma concentrations of atrial natriuretic peptide were raised at baseline but angiotensin II, aldosterone, and noradrenaline concentrations were within normal limits. There was, however, a wide interindividual variation. Plasma noradrenaline concentration and prediction score were higher among patients with class III congestive heart failure according to the New York Heart Association's classification than among patients with class II congestive heart failure ($P < 0.05$). There was a modest but significant inverse correlation between exercise duration at baseline and plasma noradrenaline concentration ($r = -0.21$, $P = 0.0023$), aldosterone concentration ($r = -0.14$, $P = 0.04$), and prediction score ($r = -0.24$, $P = 0.0004$). Prediction score at baseline was significantly higher among those who died ($n = 10$) than among survivors ($P = 0.03$). Angiotensin converting enzyme activity was suppressed and plasma concentrations of aldosterone and atrial natriuretic peptide were reduced after 12 weeks of treatment with ramipril compared with placebo. In patients with the most pronounced neurohormonal activation at baseline (highest third of noradrenaline concentration or prediction score), noradrenaline concentration and prediction score were significantly lower after 12 weeks of taking ramipril compared with placebo. Patients with a prediction score in the highest third at baseline had a higher heart rate than to those in the lowest third ($P = 0.003$).**

***Conclusions*—Neurohormonal activation is associated with the degree of symptoms and the severity of disease in mild or moderately severe congestive heart failure. Treatment with ramipril attenuates neurohormonal activation. This effect is most pronounced among patients with the highest circulating concentrations of neurohormones before the start of treatment.**

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The efficacy of treatment of congestive heart failure may be assessed in terms of symptomatic improvement, by invasively or non-invasively measured indices of cardiac performance, and by evaluating functional capacity. The use of these variables, however, seems to be of limited value in evaluating the long term efficacy of pharmacological interventions in heart failure. An improvement in exercise capacity or cardiac performance is not necessarily reflected in less progression of the disease.

Recently neurohormonal factors have emerged as important determinants of disease progression in congestive heart failure.[1] A strong relation has been found between circulating neurohormone concentrations and mortality in severe heart failure,[2] and plasma noradrenaline concentration seems to be a more sensitive guide to prognosis than traditionally measured haemodynamic variables.[3] In the first cooperative north Scandinavian enalapril survival study (CONSENSUS I) the reduction in mortality with enalapril primarily occurred among patients with high plasma concentrations of neurohormones at the start of treatment.[2] Less is known about the association of neurohormonal activation and disease progression in milder forms of heart failure, although recent data have indicated a relation between activation of neurohormonal systems and mortality in heart failure of moderate severity.[4] Despite the widespread use of angiotensin converting enzyme inhibitors in patients with mild or moderately severe heart failure, the long term effects of such treatment on the renin-angiotensin system, the sympathetic nervous system, and atrial natriuretic peptide have not been exactly defined.

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The Nordic Ramipril Trial Study Group evaluated the effects of the angiotensin converting enzyme inhibitor ramipril on exercise duration in patients with mild or moderate congestive heart failure. The addition of ramipril to treatment with diuretics did not significantly increase exercise time in this multicentre, randomised, placebo controlled study.[5] We present neurohormonal data from this trial. The main objectives were to analyse neurohormonal activation in patients with mild or moderately severe heart failure in relation to different clinical variables, and to study the effects of ramipril on circulating neurohormone concentrations in this population. In addition, the use of a probability prediction score for mortality, derived from hormonal data in the CONSENSUS I trial, was tested as a measure of the combined activity of different neurohormonal systems.

Patients and methods

PATIENTS

A total of 223 patients with mild or moderately severe congestive heart failure from 24 centres in Denmark, Finland, Norway, and Sweden were randomly allocated in a double blind fashion to treatment with ramipril or placebo for 12 weeks.[5] Patients were eligible for randomisation if they were taking a diuretic with or without digitalis and had an enlarged heart size in a chest radiograph ($\geqslant$ 600 ml/m^2 for men, $\geqslant$ 550 ml/m^2 for women) or left ventricular ejection fraction $\leqslant$ 40% estimated by echocardiography, or both. No vasodilators other than nitrates were allowed. The patients had to be able to perform a bicycle exercise test with exercise capacity restricted to the range of 4–10 minutes (corresponding to 60–120 W respectively), starting at 30 W, with stepwise increments of 10 W each minute. For patients with a body weight above 80 kg a maximum workload of 1·5 W/kg body weight was allowed. Blind treatment with the study drug was started when two consecutive exercise tests with identical exercise time had been performed and did not differ by more than 60 s. Reproducibility had to be verified in no more than four exercise tests.

The mean age of the patients was 64·5 years (range 39–79), 160 were men. One hundred and forty had class II congestive heart failure according to the classification of the New York Heart Association and 83 had class II disease. The primary cause of heart failure was considered to be coronary heart disease in 137 patients, idiopathic dilated cardiomyopathy in 49, arterial hypertension in 26, and valvar disorders in six. In four patients the primary cause of heart failure was considered to be chronic atrial fibrillation and in one patient the cause was unknown. The initial dose of ramipril or placebo was 1·25 mg once daily, which was increased weekly in two steps to 2·5 mg and 5 mg once daily. After four weeks the dose could be further increased at the decision of the investigator to 10 mg once daily. The mean (SD) daily dose of ramipril after 12 weeks was 7·9 (3·0) mg, and placebo 8·3 (2·9) mg. Of patients randomly allocated to ramipril, 69 were taking 10 mg daily at the end of the study and 31 were taking 5 mg or less.

BLOOD SAMPLING AND HORMONE ANALYSIS

Angiotensin converting enzyme activity and aldosterone concentration were determined in serum and angiotensin II, atrial natriuretic peptide, and noradrenaline concentrations in plasma. Venous blood samples were drawn after at least 30 minutes of rest in the supine position, before the start of blind treatment and after 12 weeks of treatment with the study drug. For analysis of angiotensin converting enzyme activity and aldosterone concentration 10 ml of blood were collected into an evacuated plain glass tube. The tube was left at room temperature for around 30 minutes, after which it was centrifuged for 5 minutes at 3000 rpm. For the analysis of angiotensin II and atrial natriuretic peptide concentration 10 ml of blood were collected in a tube containing an anticoagulant (EDTA), and for the analysis of noradrenaline concentration 5 ml were collected in a tube containing an anticoagulant (EDTA) and an antioxidant (glutathione). The tubes were placed in an ice bath and centrifuged within 20 minutes from sampling in a refrigerated centrifuge (4°C) for 5 minutes at 3000 rpm. The serum and plasma was transferred into disposable tubes and frozen at −20°C or lower. If samples were not analysed within one month they were stored at −70°C. Concentrations of angiotensin II, aldosterone, and atrial natriuretic peptide were analysed by radioimmunoassays at the Unit for Applied Biochemistry, Huddinge Hospital, Stockholm, Sweden. The methods have been described previously.[2] The mean (SD) reference values at the laboratory are: angiotensin II, 19(7) pmol/l (median 15 pmol/l); aldosterone, 404(208) pmol/l (median 363 pmol/l); atrial natriuretic peptide, 57(21) pg/ml (median 47 pg/ml). Angiotensin converting enzyme activity and noradrenaline were analysed at the Department of Bioanalytical Chemistry, Astra Hässle AB, Mölndal, Sweden. Angiotensin converting enzyme activity was analysed by an automated method using 3-(2-furylacryloyl)-L-phenylalanyl-glycyl-glycine as substrate.[6] Noradrenaline concentration in plasma-EDTA was analysed by liquid chromatography and electrochemical detection using alumina adsorption.[7] The investigators in charge of the neurohormone determinations were blind to the treatment groups.

STATISTICAL METHODS

The neurohormone values are presented as means (SD) unless otherwise specified. The relation between continuous variables was evaluated by the Spearman correlation coefficient. The Mann-Whitney U test was used for the non-paired comparisons between groups. Within group changes were evaluated by the Wilcoxon signed rank test. P values less than

Table 1 Hormone values and prediction scores at baseline and after 12 weeks treatment with study drug

	Placebo	Ramipril	P value*
	Angiotensin converting enzyme (μkat/l)		
Baseline:			
No of patients	102	111	
Mean (SD)	1·51 (0·57)	1·45 (0·53)	
Median (range)	1·43 (0·40–3·42)	1·35 (0·44–2·95)	>0·25
12 weeks:			
No of patients	89	100	
Mean (SD)	1·55 (0·58)	0·41 (0·38)	
Median (range)	1·48 (0·42–3·07)	0·28 (0·02–1·97)	0·0001
	Angiotensin II (pmol/l)		
Baseline:			
No of patients	104	110	
Mean (SD)	13·4 (26·6)	14·4 (18·5)	
Median (range)	7·0 (2·4–255·0)	5·4 (2·0–85·5)	>0·25
12 weeks:			
No of patients	88	98	
Mean (SD)	12·4 (28·4)	11·7 (15·5)	
Median (range)	5·8 (2·3–256·8)	5·9 (2·4–104·2)	>0·25
	Aldosterone (pmol/l)		
Baseline:			
No of patients	103	111	
Mean (SD)	418 (307)	387 (317)	
Median (range)	349 (67–2482)	393 (69–2576)	0·16
12 weeks:			
No of patients	90	100	
Mean (SD)	459 (344)	274 (165)	
Median (range)	367 (65–2370)	236 (67–1000)	0·0001
	Atrial natriuretic peptide (pg/ml)		
Baseline:			
No of patients	103	111	
Mean (SD)	256 (222)	241 (138)	
Median (range)	207 (21·9–2000)	214 (15·6–719)	>0·25
12 weeks:			
No of patients	89	100	
Mean (SD)	234 (150)	204 (123)	
Median (range)	193 (10·4–740)	180 (23·5–612)	0·25
	Noradrenaline (nmol/l)		
Baseline:			
No of patients	104	110	
Mean (SD)	2·54 (1·41)	2·69 (1·52)	
Median (range)	2·18 (0·41–10·0)	2·42 (0·8–13·0)	0·21
12 weeks:			
No of patients	89	100	
Mean (SD)	2·50 (1·27)	2·48 (0·98)	
Median (range)	2·07 (0·66–5·84)	2·33 (0·77–5·94)	>0·25
	Prediction score (%)		
Baseline:			
No of patients	103	109	
Mean (SD)	21·3 (3·0)	21·6 (3·4)	>0·25
12 weeks:			
No of patients	86	98	
Mean (SD)	21·2 (2·9)	20·9 (2·0)	>0·25

*For between group comparisons (Mann-Whitney U test).

0·05 were considered significant.

A probability prediction score for mortality was calculated from neurohormonal data in the CONSENSUS I trial database.[8] Data from four hormones were used for the analysis; angiotensin II, aldosterone, atrial natriuretic peptide, and noradrenaline. Stepwise linear discriminant analysis was used with a model including the four hormones and all possible pairs of hormones (two way interaction).[9] The stepwise procedure was based on a fixed alpha-to-enter level of 0·15.[10] The discriminant score calculated from this model was converted into a predicted probability of mortality using the formula: $P = e^x/1 + e^x$, where P is the predicted probability of mortality at six months. Among the 10 possible terms (four individual hormones and six pairs of products) two contributed significantly to the discrimination: noradrenaline and the product of angiotensin II and atrial natriuretic peptide. The model selected was x = − 1·6181 + (angiotensin II × atrial natriuretic peptide/109290) + (noradrenaline/1587), where all three hormones are measured in pg/ml.

A prediction score was calculated for each patient at baseline and after 12 weeks of treatment.

Table 2 Correlation between plasma concentrations of hormones at baseline

	Angiotensin II	Aldosterone	Atrial natriuretic peptide	Noradrenaline
Angiotensin II:				
Sample size	—	213	213	213
r	—	0·30	0·11	0·22
P value	—	0·0001	0·12	0·001
Aldosterone:				
Sample size	—	—	213	213
r	—	—	0·20	0·20
P value	—	—	0·004	0·004
Atrial natriuretic peptide:				
Sample size	—	—	—	213
r	—	—	—	0·27
P value	—	—	—	0·0001

r, Spearman correlation coefficient.

Results

Of the 223 patients who were randomised to blind treatment, 20 were withdrawn because of various adverse events (10 were taking placebo, 10 ramipril). Ten patients died (seven were taking placebo, three ramipril), two after being withdrawn from the trial (both were taking ramipril). Blood samples were available for analysis from 215 patients at baseline (104 taking placebo, 111 ramipril) and from 190 patients at 12 weeks (90 taking placebo, 100 ramipril).

NEUROHORMONAL ACTIVATION BEFORE BLIND TREATMENT

Table 1 summarises mean and median values for the different hormones and the prediction score at baseline and after 12 weeks of treatment. The concentrations of angiotensin II, aldosterone, and noradrenaline at baseline were within normal limits. However, there was generally a wide variation in neurohormonal concentrations and some patients clearly had raised values. Plasma atrial natriuretic peptide concentration at baseline was raised. A modest, but significant correlation was found between the different hormones at baseline, with r values in the range of 0·2–0·3 (table 2).

Circulating concentrations of angiotensin II, aldosterone, atrial natriuretic peptide, and noradrenaline at baseline tended to be higher among those who did not survive (n = 10) than among survivors, but this was not significant. However, prediction score at baseline was significantly higher among those who did not survive (26·1%(8·8%)) than among survivors (21·2%(2·6%)) (P = 0·03).

Plasma noradrenaline concentration and prediction score were both significantly higher among patients with class III congestive heart failure than among those with class II (figure 1). There was a significant inverse correlation at baseline between exercise time and plasma noradrenaline concentration (r = − 0·21, P = 0·0023), aldosterone concentration (r = − 0·14, P = 0·04), and prediction score (r = − 0·24, P = 0·0004) (figure 2). No relation was found

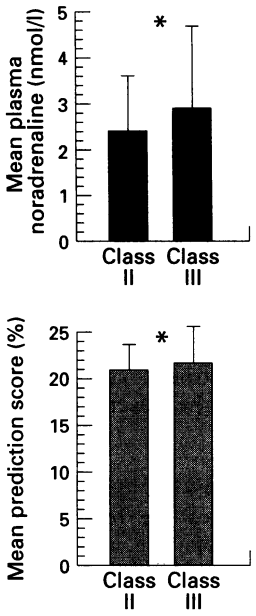

*Figure 1 Plasma noradrenaline concentration and prediction score at baseline in patients with class II (n = 136) and III (n = 78) heart failure according to the classification system of the New York Heart Association. *P < 0·05.*

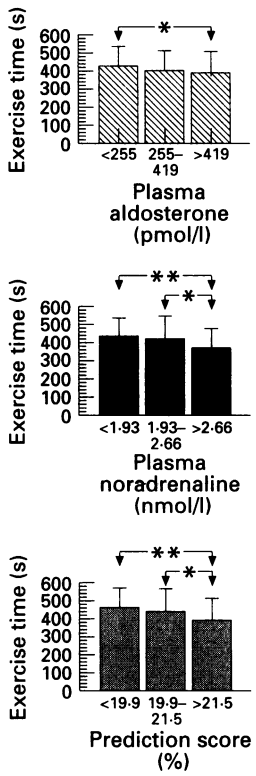

*Figure 2 Total exercise time at baseline in relation to thirds of plasma noradrenaline and aldosterone concentration and prediction score. *P < 0·05, **P < 0·01.*

Table 3 Baseline characteristics stratified by the lowest and highest third of prediction score

	Lowest (n = 73)	*Highest (n = 70)*	*P value*
Mean (SD) age (years)	63·0 (8·8)	65·3 (8·2)	NS
Systolic blood pressure (mm Hg)	136	134	NS
Diastolic blood pressure (mm Hg)	80	82	NS
Heart rate (beats/min)	69	75	0·003
S-Sodium (mmol/l)	141	140	NS
S-Creatinine (μmol/l)	93	100	0·07

S, serum.

between exercise time and plasma concentrations of angiotensin II or atrial natriuretic peptide. Table 3 shows the relation between prediction score and some clinical and laboratory variables at baseline. There was a significant difference between patients with prediction score in the highest and lowest third with respect to heart rate.

EFFECTS OF RAMIPRIL ON CIRCULATING NEUROHORMONE CONCENTRATIONS

After 12 weeks of treatment angiotensin converting enzyme activity and aldosterone concentration were significantly lower in the ramipril group compared with the placebo group (table 1). Figure 3 shows the relative changes in hormone concentrations between baseline and 12 weeks. In contrast to the data in table 1, the statistical analysis shown in figure 3 is based on paired data alone. Plasma angiotensin converting enzyme activity and aldosterone and atrial natriuretic peptide concentrations were significantly reduced in the ramipril group but unchanged in the placebo group. There were no significant changes in plasma concentrations of angiotensin II and noradrenaline or in prediction score in either group. The effects of treatment among patients with plasma noradrenaline concentration in the highest third at baseline were separately analysed. In this group plasma noradrenaline concentration was significantly lower in the ramipril group compared with the placebo group at 12 weeks (figure 4). Also, among patients with a prediction score in the highest third at baseline, the score was significantly lower in the ramipril group at 12 weeks compared with the placebo group (figure 4). The same was not true for plasma concentrations of angiotensin II. No differences between the treatment groups were found for plasma noradrenaline concentration and prediction score in the middle and lowest thirds.

Discussion

Neurohormonal mechanisms are often activated in patients with heart failure.[11–14] Other studies have shown circulating neurohormone concentrations to be highly related to mortality.[2 3 15] Neurohormonal activation is also more pronounced in acute, unstable heart failure than in the more stable, chronic form of the disorder.[16] Thus, activation of neurohormonal systems seems to be related to the severity of the underlying disease, although in patients with the same clinical severity of heart failure, neurohormonal activation may vary and still be related to mortality.[2] Our study describes neurohormonal activation in a fairly large group of patients with mild or moderately severe heart failure. There was some selection in the trial as the patients had to be able to exercise within a predefined range on a bicycle before inclusion in the study. Otherwise, the group is representative of patients with heart failure receiving diuretics and with symptoms predominantly at exercise.

HORMONE CONCENTRATIONS BEFORE BLIND TREATMENT

The mean concentrations of angiotensin II, aldosterone, and noradrenaline were within normal limits at baseline suggesting much less activation of the vasoconstrictor systems than among patients with more advanced symptoms.[2] We emphasise, however, that there was a large variation in circulating concentrations of these hormones, with some patients having very high values. Plasma concentrations of atrial natriuretic peptide were increased, which may be a reflection of the haemodynamic state.[17 18] Prediction score at baseline was significantly related to subsequent mortality, which is in accordance with the results from CONSENSUS I.[8] These results must, however, be interpreted carefully as there were only 10 deaths during the study period and because the study was not designed to assess mortality. There was a relatively weak, but significant, inverse correlation between exercise duration at baseline and noradrenaline, and aldosterone concentration as well as prediction score. A similar relation has been described for noradrenaline in a smaller study by Francis *et al.*[19] A relation was found between the severity of symptoms and plasma noradrenaline concentration as well as prediction score. Moreover, there was a correlation between the different hormone concentrations at baseline, indicating that the different neurohormonal systems tend to be activated together in the same patient; we emphasise, however, that the correlation coefficients were relatively low.

It has not been exactly defined when neurohormonal systems become activated in patients with congestive heart failure. Atrial natriuretic peptide and noradrenaline concentrations may be raised in patients with left ventricular dysfunction without overt heart failure.[20] Remes *et al* found that activation of the renin-angiotensin system is infrequent in patients with new onset heart failure without diuretic treatment.[21] Our study shows that there is large interindividual variation in neurohormonal concentrations among patients with similar clinical symptoms. Thus, despite some correlation between neurohormonal activation and symptoms, patients with stable symptomatic heart failure do not always have activated neurohormonal systems and patients with asymptomatic left ventricular dysfunction may have activated systems. This indicates that neurohormonal activation, measured as hormonal concentrations in the blood, is not a strong determinant of the

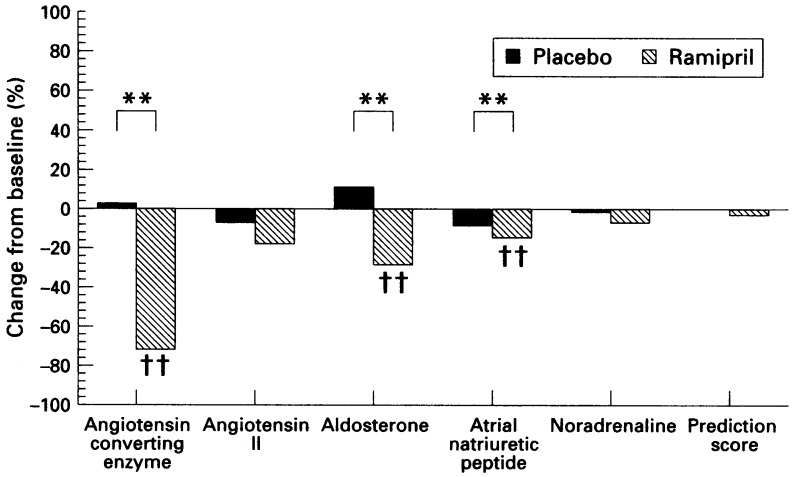

*Figure 3 Percentage changes in angiotensin converting enzyme activity, concentrations of angiotensin II, aldosterone, and atrial natriuretic peptide, and prediction score between baseline and 12 weeks. Results of the statistical analysis for within group changes are shown (†† $P < 0.01$) as well as for the comparison of the changes between the two treatment groups (** $P < 0.01$).*

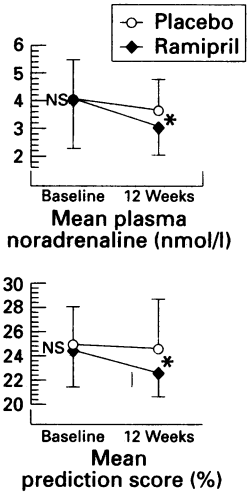

*Figure 4 Plasma noradrenaline and prediction score at baseline and 12 weeks among patients with plasma noradrenaline concentration in the highest third at baseline. Results for the between groups comparison at baseline and 12 weeks are shown. * $P < 0.05$, ns, not significant.*

severity of clinical symptoms in heart failure. On the other hand, there is evidence suggesting that neurohormonal activation is strongly related to the progressive nature of the disorder. Neurohormonal activation may be a better indicator of progressive disease than the severity of symptoms in patients with heart failure.[1 4 22]

EFFECTS OF RAMIPRIL ON NEUROHORMONAL ACTIVATION

Angiotensin converting enzyme activity and aldosterone and atrial natriuretic peptide concentrations were significantly reduced by ramipril compared with placebo, indicating compliance with treatment, interference with the renin-angiotensin aldosterone axis, and beneficial haemodynamic effects. Plasma angiotensin II concentration was not significantly reduced by ramipril treatment. In some studies angiotensin converting enzyme inhibitors reduce angiotensin II concentrations. However, these studies have mostly been done in patients with more severe or unstable heart failure in which angiotensin II concentrations before treatment were higher than in our patients.[23-27] The relatively low plasma concentrations of angiotensin II may to some degree explain why this hormone was not suppressed by ramipril in our study. Another possibility is that the reactive rise in circulating renin and angiotensin I concentrations may have overcome the inhibition of angiotensin converting enzyme activity, allowing angiotensin II concentrations to rise. Among patients taking ramipril, 69% were taking 10 mg daily and the mean daily dose was 7·9 mg. Therefore ineffective dosing is an unlikely explanation for the lack of effect on circulating angiotensin II concentration among patients receiving ramipril. Plasma noradrenaline concentration was also unaffected by ramipril. Angiotensin converting enzyme inhibitors have been found to reduce circulating concentrations of noradrenaline in patients with heart failure, although this has not been consistent and the responses may not be the same during acute and long term treatment.[28-34] In patients with the most pronounced neurohormonal activation both prediction score and plasma noradrenaline concentration were significantly lower in the ramipril group at 12 weeks compared with the placebo group. In this type of analysis a regression to the mean has to be considered, but this phenomenon cannot explain the differences between the two treatment groups. Thus, a reduction in plasma noradrenaline concentration with angiotensin converting enzyme inhibitors seems to be most easily achieved when the pretreatment values are high. This could explain the discrepancies between earlier studies.

NEUROHORMONAL PREDICTION SCORE

As several plasma hormones are related to mortality in congestive heart failure, an assessment of the combined activation of neurohormonal systems may be a better predictor of progression of heart failure and mortality than plasma concentrations of individual hormones. A probability prediction score for mortality derived by multivariate analysis of hormone data from CONSENSUS I was used to assess combined neurohormonal activity in our study. The aim was to find out if a combined nominator for the different hormonal systems can be used as a measure of severity in mild to moderate forms of congestive heart failure, and if this nominator can be affected by treatment with an angiotensin converting enzyme inhibitor. Although the selected model is the best based on data from CONSENSUS I, other models might be better in general. Therefore it is important to test such statistical models in different patient populations. In our study noradrenaline contributed relatively more to the prediction score than angiotensin II and atrial natriuretic peptide. A population of patients with high prediction score at baseline was identified as having higher heart rate, higher serum creatinine concentration, and less exercise duration, probably indicating more severe heart failure.

NEUROHORMONAL ACTIVATION AND HEART FAILURE

The determinants of neurohormonal activation in chronic heart failure are not entirely known. There seems to be clear variation in neurohormonal concentrations among patients with similar clinical symptoms; no clear relation has been found between neurohormonal activation and haemodynamic measurements.[35 36] Furthermore, neurohormonal activation may be partly related to pharmacological treatment such as with diuretics.[37-40] Whether neurohormonal activation is a reflection only of the severity of the underlying disease or whether it is an important component in the pathophysiology of chronic heart failure is not known. The positive effects of angiotensin converting enzyme inhibitors on mortality and progression of heart failure and the efficacy of β blockers in patients with heart failure due to idiopathic dilated cardiomyopathy certainly indicate that suppression of

neurohormonal activity is important.[41] A neurohormonal hypothesis has been formulated stating that prolonged activation of the sympathetic nervous system and the renin-angiotensin system exerts a direct adverse effect on the heart that is independent of the haemodynamic action of these systems.[1 42 43] Although still unproved, this hypothesis may have important implications for future treatment of congestive heart failure, as persistent activation of different autocrine, paracrine, and endocrine systems in itself becomes a therapeutic target.

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