were measured as an index of lipid intake,¹⁷ and their distribution agreed with those recently reported.^{18 19}

The results emphasise the relation between consumption of alcohol and the relative proportion of palmitoleic, oleic, and linoleic acids in the plasma cholesterol esters of a group of healthy middle aged men. They agree with the finding of a higher proportion of monounsaturated fatty acids and a lower proportion of linoleic acid in human alcoholic fatty liver.⁴⁻⁷ The apparently stronger association of consumption of alcohol with palmitoleic acid than with the other cholesterol esters is consistent with the observation that the proportion of this fatty acid in adipose tissue best differentiates alcoholics from non-alcoholics.⁷ The association between consumption of alcohol and the pattern of fatty acids in cholesterol esters may reflect the stimulation of hepatic acid biosynthesis^{2 3 20} or the change in 6-desaturase activity induced by alcohol^{21 22} rather than a different intake of fat in subjects drinking alcohol, as suggested by the results of the multiple regression analysis (table III).

The implications of these observations are twofold. Firstly, as palmitoleic acid appears to be an independent marker of consumption of alcohol it could be used in epidemiological or clinical studies together with other markers to compute a composite index of consumption even though its determination is rather tedious. Secondly, in studies in man consumption of alcohol should always be controlled when the relations between the fatty acids of serum cholesterol esters (and probably of other lipid components) and biological variables or conditions are investigated.

These results may help to improve understanding of the relation between the intake of lipids and alcohol and coronary heart disease, but this will depend on the effectiveness of the prospective information from this study.

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Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin

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Abstract

Nineteen patients with chronic heart failure participated in a double blind crossover trial of captopril and prazosin—two drugs with differing neuroendocrine effects—to determine whether neuroendocrine changes could ex-

plain clinical and haemodynamic responses to treatment. Patients were assessed before and after acute and long term (four weeks) treatment with each drug given in random order. Sixteen patients completed the study.

During captopril haemodynamic improvement was maintained by inhibition of the renin-angiotensin system. Breathlessness was relieved in 15 patients and exercise capacity increased. During prazosin a reduction in systemic vascular resistance was maintained, but plasma renin activity and aldosterone and noradrenaline concentrations increased, fluid retention developed, and clinical benefit did not occur.

These results suggest that clinical and haemodynamic responses to long term vasodilator treatment for chronic heart failure are related to neuroendocrine changes. In patients with chronic heart failure inhibition of the renin-angiotensin system results in clinical benefit, whereas inhibition of the α adrenergic system does not.

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Introduction

In heart failure vasodilator drugs increase cardiac output and reduce ventricular filling pressures acutely.^{1,2} Continued treatment with these drugs does not always result in prolonged clinical benefit. Loss of clinical effect may be due to progression of the underlying heart disease or to the development of "tolerance," which occurs with many vasodilators.³⁻⁵ A possible cause of tolerance is that the underlying neuroendocrine abnormalities of heart failure play an important part in determining the clinical features and long term outcome,⁶ and that vasodilator treatment may exacerbate these abnormalities.^{7,8}

The renin-angiotensin-aldosterone system and sympathetic nervous system are activated in heart failure,⁶ causing vasoconstriction and fluid retention. Captopril has been used to inhibit the renin-angiotensin-aldosterone system in these patients,⁹ while prazosin has been used to inhibit the α_1 adrenoreceptors of the sympathetic system.¹⁰ Acute administration of these agents causes similar venous and arteriolar vasodilatation by withdrawal of neuroendocrine vasoconstriction.¹¹

We report the first double blind, randomised crossover study of the acute and long term responses to captopril and prazosin in patients with chronic heart failure, thereby examining the relation between alterations in neuroendocrine systems and clinical and haemodynamic responses to vasodilator treatment.

Patients and methods

Nineteen patients were studied. Their mean age was 62 years (range 48-74), and 18 were men. All patients had been in heart failure for at least three months. The aetiology of the heart failure was coronary heart disease without recent myocardial infarction in 13 patients and dilated cardiomyopathy in six. No patient had appreciable valvular, hypertensive, or renal disease.

All patients were breathless on moderate exertion, with radiological pulmonary venous hypertension and cardiomegaly (cardiothoracic ratio >0.5) despite optimal treatment with diuretics. The mean daily dose of frusemide was 135 mg combined with amiloride 9 mg. Only the four patients who were in atrial fibrillation received digoxin for control of ventricular rate. Other vasodilators, or spironolactone, were not used during the study. All patients gave written, informed consent. The study was approved by the hospitals' ethical committees.

STUDY DESIGN

The study was in three phases: a run in control period, an acute haemodynamic study, and a study of long term effects. Patients were observed in hospital for one week in the control period taking diuretics and placebo to ensure that they remained in a stable clinical state with constant body weight and without peripheral oedema. They were

then randomised for the acute haemodynamic study, in which they received a single oral dose of captopril 25 mg on one day and prazosin 2 mg on the next (or vice versa), given double blind four hours after their diuretic. Measurements were made before and after these acute doses (see below). The chosen doses of captopril and prazosin have been shown to produce similar acute haemodynamic effects.¹¹

The patients were then randomised again for long term treatment and immediately began captopril or prazosin double blind. The doses used were captopril 25 mg eight hourly or prazosin 2 mg eight hourly for the first week and double this dose for the rest of each month. After one month clinical, haemodynamic, and neuroendocrine measurements were repeated before and after the second daily maintenance dose of drug (captopril 50 mg or prazosin 4 mg). Each patient then crossed over, without a washout period, to a month of treatment with the other drug and measurements were repeated at the end of the second month. The initial control dose of diuretics was maintained throughout the study, unless peripheral oedema developed with weight gain of 2.5 kg or more, in which case the dose of frusemide was increased for the remainder of that month's treatment period only.

CLINICAL ASSESSMENT

Clinical features were assessed daily during the control period and then at one and four weeks of each treatment period. Exercise capacity was assessed on a treadmill using a protocol with low workloads, increasing in six minute stages.¹² Patients performed preliminary exercise tests during the control period until they achieved consistent maximal exercise. Maximal exercise time was measured at the end of the control period and again at the end of each month's treatment period.

HAEMODYNAMIC MEASUREMENTS

Patients were studied while resting in bed. Standard right heart monitoring techniques were used.¹³ Pulmonary artery end diastolic pressure was used as an indirect measure of left ventricular filling pressure. Blood pressure was measured by sphygmomanometer ($n=13$) or brachial artery catheter ($n=6$). Heart rate was measured from a simultaneous electrocardiogram. Systemic vascular resistance and cardiac index were calculated by standard formulas.

Control measurements were made at 30 minute intervals before each study to assess haemodynamic stability. Either captopril or prazosin was then given, as above, and measurements made hourly for four hours. The control value immediately before each initial acute dose was used as the pretreatment control. Values before the maintenance dose during long term treatment are "trough" values, just before the second daily dose of the drug.

NEUROENDOCRINE MEASUREMENTS

Venous blood was sampled with the patient resting in bed, immediately before and two hours after each initial drug dose and at a

TABLE 1—Initial acute haemodynamic effects. Results expressed as mean (95% confidence limits) before drug (time zero) and for four hours after first dose of captopril and prazosin

	Time zero	Hours after first dose			
		1	2	3	4
Captopril 25 mg					
Pulmonary artery end diastolic pressure (mm Hg)	21 (18-25)	14 (10-17)***	15 (11-18)***	16 (13-19)**	18 (13-21)**
Right atrial pressure (mm Hg)	8 (5-11)	5 (2-7)***	5 (3-8)**	6 (3-9)*	7 (4-9)
Cardiac index (l/min/m ²)	2.1 (1.9-2.2)	2.3 (2.1-2.5)**	2.4 (2.2-2.6)**	2.3 (2.1-2.4)*	2.2 (2.0-2.4)
Stroke volume index (ml/min/m ²)	24.0 (21.0-27.0)	29.7 (25.3-34.2)**	30.3 (27.0-33.6)***	27.8 (24.4-31.1)**	25.5 (22.4-28.7)
Heart rate (beats/min)	90 (83-96)	82 (75-89)**	80 (74-87)**	84 (78-91)**	88 (81-94)
Systemic vascular resistance (dyn s/cm ²)	1645 (1476-1813)	1199 (1044-1354)***	1175 (999-1351)***	1294 (1110-1478)**	1407 (1209-1605)*
Systolic blood pressure (mm Hg)	110 (103-117)	89 (81-96)***	88 (80-95)***	95 (85-104)**	94 (87-101)**
Diastolic blood pressure (mm Hg)	70 (65-75)	57 (51-63)**	56 (49-62)**	59 (53-66)**	62 (55-68)*
Prazosin 2 mg					
Pulmonary artery end diastolic pressure (mm Hg)	20 (17-24)	18 (15-22)*	15 (12-19)**	16 (12-19)**	16 (13-20)**
Right atrial pressure (mm Hg)	7 (4-10)	6 (4-9)	5 (2-9)	5 (2-8)	5 (3-8)
Cardiac index (l/min/m ²)	2.0 (1.8-2.2)	2.2 (2.0-2.4)*	2.1 (1.9-2.3)	2.2 (2.1-2.4)	2.3 (2.1-2.4)
Stroke volume index (ml/min/m ²)	23.8 (20.5-27.0)	24.8 (21.6-28.1)*	24.3 (21.1-27.6)	25.0 (22.6-27.4)	26.4 (24.1-28.7)
Heart rate (beats/min)	89 (83-96)	89 (83-96)	88 (83-94)	91 (84-98)	88 (82-94)
Systemic vascular resistance (dyn s/cm ²)	1678 (1492-1864)	1561 (1337-1786)	1565 (1320-1809)	1509 (1295-1723)	1415 (1235-1595)*
Systolic blood pressure (mm Hg)	104 (100-109)	100 (93-107)	97 (91-102)**	101 (94-107)	101 (95-107)
Diastolic blood pressure (mm Hg)	70 (65-74)	66 (60-72)	63 (59-68)**	66 (61-70)*	64 (58-70)*

Compared with time zero: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

trough period after one week and one month's treatment with each drug. Measurements were made of plasma renin activity¹⁴ and aldosterone concentration^{14 15} (normal ranges with a sodium intake of 100-200 mmol(mEq)/24 h being 0.5-2.5 ng/ml/h and 100-600 pmol/l (36-216 pg/ml), respectively), plasma noradrenaline concentration¹⁶ (normal range 1.2-4.7 nmol/l (200-800 pg/ml)), and plasma vasopressin concentration¹⁷ (normal range 0.4-1.6 mU/l).

PLASMA DRUG CONCENTRATIONS

Plasma captopril concentrations were not measured: increasing plasma renin activity was used as an indicator of effective converting enzyme inhibition. Plasma prazosin concentration was measured by

FIG 1—Relation of cardiac index to pulmonary artery end diastolic pressure in acute and long term studies. Mean values shown from control to peak effect after single dose. (See tables I and III for variability and statistical results.)

TABLE II—Neuroendocrine results. Results expressed as geometric mean (95% confidence limits) of control value and absolute changes (95% confidence limits) two hours after acute dose and after one week and one month of captopril and prazosin

	Control value	2 hours	1 week	1 month
Captopril				
Plasma renin activity (ng/ml/h)	7.24 (4.9-10.7)	+20.26 (+14.53, +26.0)***	+9.66 (+4.55, +14.77)**	+6.21 (+2.39, +10.03)**
Plasma aldosterone (pmol/l)	690 (520-917)	-360 (-520, -201)**	-197 (-392, -2)*	-240 (-475, -6)*
Plasma noradrenaline (nmol/l)	5.4 (4.2-7.0)	-0.09 (-0.84, +0.65)	-0.08 (-1.76, +1.59)	-0.69 (-1.91, +0.53)
Plasma vasopressin (mU/l)	0.81 (0.57-1.15)	+0.07 (-0.48, +0.62)	+0.13 (-0.37, +0.63)	-0.14 (-0.58, +0.31)
Prazosin				
Plasma renin activity (ng/ml/h)	7.24 (4.9-10.7)	+2.53 (+0.01, +5.06)*	+2.16 (-2.0, +6.32)	-2.68 (-5.14, -0.23)*
Plasma aldosterone (pmol/l)	690 (520-917)	+16 (-120, +152)	+296 (+150, +441)**	+207 (-141, +557)
Plasma noradrenaline (nmol/l)	5.4 (4.2-7.0)	+1.09 (+0.40, +1.78)**	+2.19 (+0.24, +4.15)*	+1.57 (+0.05, +3.07)*
Plasma vasopressin (mU/l)	0.81 (0.57-1.15)	-0.15 (-0.54, +0.24)	+0.05 (-0.13, +0.23)	-0.03 (-0.41, +0.33)

Compared with pretreatment control value: *p<0.05; **p<0.01; ***p<0.001.
Conversion: SI to traditional units—Aldosterone: 1 pmol/l ≈ 0.36 pg/ml. Noradrenaline: 1 nmol/l ≈ 169 pg/ml.

high performance liquid chromatography.¹⁸ Measurements were made in eight patients after one month's treatment before and two hours after a 4 mg maintenance dose.

STATISTICS

The trial was designed to detect a change in pulmonary artery end diastolic pressure of 5 mm Hg at the 5% level of significance during either treatment period with a power of 0.80,¹⁹ based on data obtained in a pilot study in similar patients. Statistical analysis^{19 20} was by analysis of variance, Student's *t* tests for paired or unpaired data, as appropriate, and linear regression. Results are given as the means and 95% confidence limits. Logarithmic transformations were applied to hormonal measurements.

Initial analysis²¹ showed that order of treatment did not influence the magnitude of changes in body weight, exercise time, or hormonal values, so changes due to treatment with a drug in the first period were combined with changes due to that drug in the second period to give a value of overall change.

Results

ACUTE STUDY

The mean pretreatment left ventricular filling pressure was 21 mm Hg (95% confidence limits 18, 25) and the cardiac index 2.1 l/min/m² (1.9, 2.2). The acute haemodynamic effects of captopril and prazosin were similar (fig 1; table I). Both drugs reduced left and right ventricular filling pressures, systemic vascular resistance, and blood pressure while increasing the cardiac index. Only captopril reduced the heart rate. The effects of captopril were maximal after one to two hours, while those of prazosin were of slower onset. The acute haemodynamic effects of captopril did not correlate with the pretreatment plasma renin activity. The pretreatment plasma renin activity and aldosterone and noradrenaline concentrations were raised; plasma vasopressin was normal in these patients (table II). The pretreatment plasma renin activity and aldosterone and noradrenaline values correlated with the pretreatment left ventricular filling pressure (*r*=0.53, *p*=0.02; *r*=0.46, *p*=0.04; *r*=0.6, *p*=0.01, respectively).

Inhibition of angiotensin converting enzyme by captopril increased the plasma renin activity and reduced the plasma aldosterone concentration to normal two hours after the first dose. Despite the reduction in arterial pressure plasma noradrenaline was unchanged. Inhibition of α adrenoceptors by prazosin increased plasma renin activity and noradrenaline values two hours after the first dose. Plasma vasopressin was not changed by either drug.

LONG TERM STUDY

During long term treatment three patients were withdrawn, two because of symptomatic hypotension (one taking captopril, one prazosin) and one because of non-compliance (receiving prazosin). No other adverse effects occurred. Sixteen patients completed the two month crossover study.

While taking captopril 15 patients improved symptomatically and one was unchanged. Mean weight fell by 1.6 kg (95% confidence limits -3.2, -0.1; *p*=0.05) after one month without any increase in diuretic dosage (fig 2). During the prazosin period only five

patients improved symptomatically, three were unchanged, and eight deteriorated; peripheral oedema developed in six patients. Mean weight increased by 2.8 kg (0.4, 5.2; *p*=0.03) despite increasing the frusemide dosage in four patients who developed oedema after one week (fig 2).

Treadmill exercise time at the end of the placebo period was 17.5 minutes (12.0, 23.0). Captopril increased exercise time by 6.2 minutes (3.0, 9.5; *p*=0.0012) but prazosin had no effect (+0.7 minute; 95% confidence limits -5.7, 7.0; *p*=0.81).

After one month of captopril the acute reduction in ventricular filling pressures and heart rate were maintained (fig 1; table III). Left ventricular filling pressure was 16 mm Hg (13, 20), falling to 14 mm Hg (10, 17) two hours after a maintenance dose, which also reduced systemic vascular resistance and blood pressure and increased the cardiac index. By contrast, long term prazosin failed to maintain the acute reduction in left and right ventricular filling pressures. The maintenance dose did not reduce filling pressures or increase cardiac index significantly, but systemic vascular resistance and diastolic blood pressure were reduced.

During long term captopril plasma renin activity was increased

TABLE III—Haemodynamic effects after long term treatment. Results expressed as mean (95% confidence limits) before (time zero) and for four hours after maintenance dose of captopril and prazosin during long term treatment

	Time zero	Hours after maintenance dose			
		1	2	3	4
Captopril 50 mg					
Pulmonary artery end diastolic pressure (mm Hg)	16 (13-20)††	14 (10-18)*††	14 (10-17)*††	15 (12-19)††	15 (12-18)††
Right atrial pressure (mm Hg)	6 (3-9)	4 (2-7)†	4 (2-6)††	5 (2-7)†	5 (2-7)†
Cardiac index (l/min/m ²)	2.1 (2.0-2.3)	2.3 (2.1-2.5)	2.3 (2.1-2.5)	2.5 (2.1-2.9)*†	2.4 (2.1-2.6)*†
Stroke volume index (ml/min/m ²)	26.9 (23.1-30.6)	29.5 (26.1-32.9)*††	30.1 (25.9-35.2)†	31.2 (24.8-37.6)†	29.3 (25.4-33.3)†
Heart rate (beats/min)	81 (76-87)†	80 (74-86)†	77 (70-84)††	81 (75-87)†	81 (75-87)†
Systemic vascular resistance (dyn s/cm ⁵)	1549 (1368-1730)	1366 (1192-1541)*††	1432 (1156-1708)†	1344 (1115-1572)*††	1425 (1170-1680)†
Systolic blood pressure (mm Hg)	103 (96-110)	96 (89-102)*††	97 (90-103)*††	99 (92-107)†	101 (95-107)†
Diastolic blood pressure (mm Hg)	66 (61-71)	62 (56-68)*†	62 (58-66)*††	62 (56-67)*††	63 (58-68)†
Prazosin 4 mg					
Pulmonary artery end diastolic pressure (mm Hg)	21 (17-24)	20 (16-24)	19 (15-23)	19 (15-26)	20 (16-23)
Right atrial pressure (mm Hg)	7 (4-11)	8 (4-11)	7 (4-11)	7 (3-10)	8 (4-11)
Cardiac index (l/min/m ²)	2.1 (1.9-2.3)	2.2 (2.0-2.5)	2.2 (2.0-2.4)	2.3 (1.9-2.6)	2.3 (2.1-2.5)
Stroke volume index (ml/min/m ²)	25.4 (21.4-29.4)	27.5 (23.7-31.3)	28.1 (24.3-32.0)†	28.1 (23.3-32.9)†	27.6 (24.3-31.0)†
Heart rate (beats/min)	85 (79-92)	84 (77-91)	81 (75-88)†	84 (77-92)	85 (78-93)
Systemic vascular resistance (dyn s/cm ⁵)	1534 (1298-1770)	1397 (1231-1563)†	1359 (1221-1497)††	1338 (1171-1506)†	1390 (1261-1518)†
Systolic blood pressure (mm Hg)	103 (95-110)	102 (98-105)	101 (94-107)	101 (96-106)	106 (102-111)
Diastolic blood pressure (mm Hg)	68 (62-73)	67 (62-72)	64 (59-68)*††	63 (59-68)†	67 (63-71)

Compared with time zero: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
Compared with pretreatment control value: † $p < 0.05$; †† $p < 0.01$.

and the plasma aldosterone concentration reduced to normal (fig 2; table II). Captopril also tended to reduce the plasma noradrenaline value, but the overall change in the group did not achieve statistical significance ($p = 0.15$). The changes in plasma noradrenaline concentration after one month were correlated with the long term reduction of plasma aldosterone by captopril ($r = 0.66$; $p = 0.01$).

The changes in weight during one month's treatment with captopril and prazosin correlated with the corresponding changes in plasma aldosterone concentration at one week ($r = 0.48$; $p = 0.007$). Changes in pulmonary artery end diastolic pressure during long term captopril were correlated with the changes in plasma aldosterone and noradrenaline values at one month ($r = 0.46$; $p = 0.009$).

Plasma vasopressin concentrations did not change significantly during either treatment period.

After one month's treatment the mean plasma prazosin concentration before a maintenance dose was $29.2 \mu\text{g/l}$ (18, 41). This increased to $40.4 \mu\text{g/l}$ (29, 52; $t = 2.87$; $p = 0.02$) two hours after a 4 mg dose. These plasma concentrations are high.

Discussion

The sympathetic and renin-angiotensin-aldosterone systems are activated in chronic heart failure in order to maintain the blood pressure when cardiac output is reduced.^{21 22} Although some improvement in ventricular performance may be obtained by sympathetic activation, there is widespread vasoconstriction of the renal, splanchnic, and cutaneous circulations, mediated by α adrenoceptors and angiotensin II. Reduced renal perfusion, intrarenal vasoconstriction, and increased plasma aldosterone concentrations lead to fluid retention. Directly acting vasodilators may reduce ventricular filling pressures and increase cardiac output acutely, but if blood pressure falls further homeostatic neuroendocrine activation may occur, counteracting the response to such treatment. The use of specific neuroendocrine inhibitors is theoretically attractive, since vasodilatation would occur by withdrawal of the vasoconstrictive forces.

We performed this double blind, randomised crossover comparison of two such drugs—captopril and prazosin, which have been used in the treatment of heart failure^{9 10}—in order to investigate the relations between clinical, haemodynamic, and neuroendocrine responses to long term vasodilator treatment.

Prazosin, an α_1 adrenergic antagonist, causes venous and arterial dilatation by reducing sympathetic vasoconstriction, but loss of effect may occur during long term use.⁸ In studies where the haemodynamic effects persisted patients required increasing doses of diuretics or the addition of spironolactone,^{23 24} suggesting that fluid retention is a main cause of the tolerance to prazosin.

Captopril, a converting enzyme inhibitor, prevents the for-

mation of angiotensin II and causes similar acute systemic haemodynamic effects as well as specific renal vasodilatation,²⁵ reduction in plasma aldosterone concentration, and attenuation of sympathetic noradrenergic vasoconstriction.²⁶ Such widespread effects highlight the fundamental importance of the renin-angiotensin-aldosterone system in circulatory regulation.

FIG 2—Absolute changes in plasma renin activity, aldosterone and noradrenaline concentrations, and body weight during treatment with captopril (■) and prazosin (□). Mean values (95% confidence bar) shown two hours after acute dose and after one week and one month of long term treatment. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

Conversion: SI to traditional units—Aldosterone: 1 pmol/l $\approx$ 0.36 pg/ml. Noradrenaline: 1 nmol/l $\approx$ 169 pg/ml.

Our study shows that long term inhibition of the renin-angiotensin-aldosterone system in patients with chronic heart failure results in sustained haemodynamic and clinical benefit. During captopril treatment systemic vasodilatation was maintained, as was the increase in cardiac output, while ventricular filling pressures fell to near normal. Exercise capacity increased and 15 of the 16 patients were less breathless. General wellbeing was reported frequently and may have been due to improved cerebral blood flow.²⁷ Over the same period the plasma aldosterone concentration fell to normal in all patients, facilitating natriuresis, and body weight fell. Improvement in renal perfusion also occurred with captopril,²⁸ further enhancing diuresis. A diuretic effect of captopril is not uncommon and often allows the dose of diuretics to be reduced.

Despite the sustained reduction in blood pressure during treatment with captopril plasma noradrenaline concentration and heart rate tended to fall, suggesting that the reduction in angiotensin II had decreased sympathetic activity.²⁹ Withdrawal of sympathetic venoconstriction after sustained inhibition of the renin-angiotensin-aldosterone system may, in part, explain how captopril is so effective at reducing ventricular filling pressures. There was no evidence of long term attenuation of the effects of captopril. The gradual decline in plasma renin activity during captopril probably reflects improved renal perfusion.²⁸

Long term α_1 adrenoceptor inhibition with prazosin caused sustained arteriolar vasodilatation, as shown by the reduction in systemic vascular resistance at one month. Venodilatation may also have been maintained, since filling pressures at one month were no higher than control values despite fluid retention of 2.8 kg.

Despite the maintained vasodilatation with prazosin there was no clinical benefit, and eight of the 16 patients deteriorated. There was evidence of further activation of the renin-angiotensin-aldosterone and sympathetic systems, with increases in plasma renin activity and aldosterone and noradrenaline concentrations. Plasma renin activity and aldosterone, having increased initially, causing fluid retention, were later relatively suppressed by circulatory expansion, though still remaining abnormally raised. Increasing the dose of frusemide in four patients during the prazosin treatment period did not prevent fluid retention. Other studies have shown similar hormonal increases with prazosin.^{23 30 31}

Plasma vasopressin concentrations were normal in our patients. Other studies have reported concentrations to be raised in more advanced chronic heart failure.³² Even a normal plasma vasopressin concentration might exert a vasoconstrictive effect in the presence of an activated renin-angiotensin-aldosterone system and increased angiotensin II, since the latter potentiates the vascular effects of vasopressin.²⁹

Our findings show that sustained inhibition of the renin-angiotensin-aldosterone system in patients with chronic heart failure results in vasodilatation without secondary neuroendocrine activation and is associated with prolonged clinical benefit. In contrast, although inhibition of α_1 adrenoceptors causes some vasodilatation, there is secondary activation of both the sympathetic and renin-angiotensin-aldosterone systems, which is associated with fluid retention and loss of clinical effect.

This study shows the fundamental importance of neuroendocrine systems in chronic heart failure. Inhibition of the renin-angiotensin system results in clinical benefit, whereas inhibition of the α adrenergic system does not.

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I told you before that the skins which the Greeks (and our Rabbies from them) call Amnios and Allantois contained the urin and sweat of the Child, the use of which urin and sweat is great before, and in Travel. First, before Travel, by their means the Child is more easily sustained and borne up in the Womb.

Secondly, in the time of Travel (the Birth approaching) both these skins, the Amnios and Allantois are broken by the vehement stirring of the Child, so that these excrements fall down to the neck of the Womb, and this is that Midwives call the Water, and when they see that come away, then they say to them that stand by, Now the birth is near. And tis very true, and the certainest sign that can be; for the Child is no better able long to subsist in the Womb after those skins are broken, than a naked man is in a heap of snow. These Waters, if the child come presently after them, facilitate the labour, by making the passage slippery; and therefore let no Midwives endeavour with their nails, nor anything else to force Water away. Dame Nature knows when the true time of the birth is, better than they, and usually retains the Water until that time.

On the contrary, if the Water by accident break away too long before the birth, such things as hasten Nature may be safely given or admitted; such as Dittany, Bettony, Pennyroyal, Juniper-berries, red Coral &c.

Nicholas Culpeper (1616-54)
Directory for Midwives, 1671