The renal response to neuroendocrine inhibition in chronic heart failure: double-blind comparison of captopril and prazosin

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Activation of the renin-angiotensin and sympathetic systems in chronic heart failure causes important renal vasoconstriction. In a double-blind cross-over study, treatment with captopril for one month reduced systemic and renal vascular resistance by 14% and 25%, increased renal blood flow by 12%, and increased the percentage of the cardiac output perfusion to the kidney by 13%. Treatment with prazosin for one month also reduced systemic vascular resistance by 8%, renal vascular resistance increased by 20%, and renal blood flow and the percentage of the cardiac output going to the kidney fell by 14% and 26%. During captopril treatment, plasma aldosterone concentration was reduced to normal, but during prazosin treatment there was an initial increase in aldosterone of 45%, and a sustained increase in plasma noradrenaline concentration of 26%. Body weight decreased by 1.7 kg on captopril, but increased by 3.0 kg on prazosin, correlating inversely with the changes in renal blood flow. Sympathetic inhibition with prazosin causes systemic vasodilatation which diverts blood from the kidney and may result in fluid retention. Inhibition of the renin system with captopril causes preferential renal vasodilatation and can improve renal perfusion in chronic heart failure.

Introduction

In chronic heart failure the sympathetic and renin-angiotensin-aldosterone systems are activated, as homeostatic mechanisms to support the failing circulation. Such neuroendocrine activation causes systemic and renal vasoconstriction and redistribution of blood flow away from the kidneys. Reduced renal perfusion leads to fluid retention and maintains the activation of the renin-angiotensin system and thus is an important cause of systemic vasoconstriction, persistent left ventricular impairment, and the clinical features of chronic heart failure.

We have used captopril, an inhibitor of the renin-angiotensin system, and prazosin, an alpha-adrenoceptor antagonist, to examine the interrelationships between renal perfusion, neuroendocrine activation and clinical state in chronic heart failure, in a double-blind randomized cross-over study. This report emphasizes the renal response to such neuroendocrine inhibition, other results from this study, for example the haemodynamic changes at rest and on exercise, have been reported elsewhere.

Patients and methods

Patients

Fifteen patients were studied. Their mean age was 63 years (range 48 to 74 years), 14 were male. All patients had been in heart failure for at least three months. The aetiology of heart failure was coronary artery disease, without recent myocardial infarction, in 10 patients, and dilated cardiomyopathy in 5. No patient had significant valvular, hypertensive or renal disease.

All patients were breathless on moderate exertion (NYHA class II–III), with radiological pulmonary venous hypertension and cardiomegaly (cardio-thoracic ratio >0.5), despite optimal diuretic treatment. The mean daily dose of frusemide was 117 mg combined with amiloride 9 mg. Only the two patients in atrial fibrillation received digoxin for control of ventricular rate. Other vasodilating drugs, or spironolactone, were not used during the study. All patients gave written informed consent.

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The study was approved by the hospitals' ethical committees.

STUDY DESIGN

Patients were admitted to hospital for observation during a one week control period, on diuretics and placebo, to ensure they were in a stable clinical state with constant body weight and without peripheral oedema.

At the end of this run-in period, control measurements were made, as outlined below. Patients were randomized and commenced outpatient treatment with either captopril 25 mg eight hourly or prazosin 2 mg eight hourly, given double-blind by the double-dummy technique; these doses were doubled after one week. The chosen doses have been shown to produce similar acute haemodynamic effects, and correspond to those often used in clinical practice.

After one month patients were readmitted, and all measurements were repeated, at least two hours after the morning medication. Each patient then crossed over, without a washout period, to a month of outpatient treatment with the other drug, and measurements were repeated as above 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 FEATURES

The patients' symptoms were recorded by questionnaire in the control period, and after one week and one month of each treatment period. During the control period clinical examination and measurement of nude weight were performed daily, and these were repeated after one week and one month of each treatment period.

RENAL MEASUREMENTS

Renal plasma flow and glomerular filtration rate were measured by standard radioisotope techniques, using bolus injections of $^{123}$iodohippurate and 99m Tc DTPA, respectively. The variability of replicate measurements is 5% and 8%, respectively. Filtration fraction was calculated as glomerular filtration rate/renal plasma flow. Renal blood flow (ml min$^{-1}$) was calculated as renal plasma flow/(1-haematocrit). Renal vascular resistance (dyne s cm$^{-5}$) was calculated as (mean arterial pressure/renal blood flow) × 80000. The percentage of the cardiac output perfusing the kidneys was calculated, using cardiac output measurements made at the time of renal measurements, as (renal blood flow (l min$^{-1}$)/cardiac output) × 100.

HAEMODYNAMIC MEASUREMENTS

Patients were studied lying in bed, using standard right heart haemodynamic monitoring techniques. Cardiac output was measured by thermodilution, using the mean of at least three readings with less than 10% variation. Total systemic vascular resistance (dyne s cm$^{-5}$) was calculated as 80 × (mean arterial pressure — right atrial pressure)/cardiac output.

NEUROENDOCRINE MEASUREMENTS

Plasma renin activity, aldosterone and noradrenaline were measured at rest during the control haemodynamic study and during the studies at the end of each month's treatment period. Measurements were also made after one week of each treatment, when samples were taken at rest two hours after a maintenance dose of that month's drug. Venous blood was taken without stasis into chilled bottles, centrifuged immediately, and the plasma stored at −70°C until assayed.

Plasma renin activity and aldosterone were measured by radioimmunoassay (normal ranges: 0.5–2.5 ng ml$^{-1}$ h$^{-1}$ and 100–600 pmol 1$^{-1}$, respectively).

Plasma noradrenaline was measured by radioenzymatic assay, using a modification (P. Sever, personal communication) of Henry's method (normal range: 200–800 pg ml$^{-1}$).

BIOCHEMICAL MEASUREMENTS

Plasma sodium, potassium, creatinine and blood urea were measured during the control period, and after one week and one month of each treatment period. Twenty-four hour urinary sodium excretion was measured at the end of the control and treatment periods, to determine if sodium intake had remained stable during the study.

Plasma prazosin was measured by HPLC in 8 patients, after one month's treatment, before and 2 hours after a 4 mg maintenance dose.

STATISTICS

Statistical analysis was by analysis of variance, paired and unpaired t tests, and linear regression, as appropriate. Results are given as mean (95% confidence limits). Logarithmic transformations were applied to hormonal measurements.
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Table I  Neuroendocrine results: Control body weight and neuroendocrine values, and absolute changes after one month of captopril and prazosin, in 15 patients [geometric mean (95% confidence limits)]

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Captopril 1 week</th>
<th>Captopril 1 month</th>
<th>Prazosin 1 week</th>
<th>Prazosin 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>70-4</td>
<td>-1.14**</td>
<td>-1.75*</td>
<td>+0.6</td>
<td>+2.97*</td>
</tr>
<tr>
<td></td>
<td>(62-0, 78-9)</td>
<td>(-1-8, -0-5)</td>
<td>(-3-5, -0-01)</td>
<td>(0-5, 1-7)</td>
<td>(0-7, 5-3)</td>
</tr>
<tr>
<td>PRA (ng ml⁻¹ h⁻¹)</td>
<td>6-4</td>
<td>+10.0**</td>
<td>+6.1**</td>
<td>-1.2</td>
<td>-3.1*</td>
</tr>
<tr>
<td></td>
<td>(4-1, 10-0)</td>
<td>(4-6, 15-5)</td>
<td>(2-0, 10-3)</td>
<td>(-3.3, 0.9)</td>
<td>(-5.6, -0.6)</td>
</tr>
<tr>
<td>P. aldosterone (pmol litre⁻¹)</td>
<td>697</td>
<td>-40*</td>
<td>-278*</td>
<td>+313**</td>
<td>+238</td>
</tr>
<tr>
<td></td>
<td>(483, 1007)</td>
<td>(-253, -27)</td>
<td>(-515, -41)</td>
<td>(162, 465)</td>
<td>(-131, 607)</td>
</tr>
<tr>
<td>P. noradrenaline (pg ml⁻¹)</td>
<td>892</td>
<td>-14</td>
<td>-131</td>
<td>+383*</td>
<td>+233*</td>
</tr>
<tr>
<td></td>
<td>(642, 1239)</td>
<td>(-324, 297)</td>
<td>(-352, 89)</td>
<td>(27, 739)</td>
<td>(23, 443)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.0001.

Results

CLINICAL EFFECTS

While on captopril, 14 patients improved symptomatically, reporting a reduction in breathlessness, an increase in exercise capacity and general well-being; one patient was unchanged. Mean weight fell by 1.75 kg (P=0.04) after one month (Table 1), without any increase in diuretic dosage.

On prazosin, five patients reported initial symptomatic improvement, three were unchanged and seven deteriorated. Peripheral oedema developed in six patients. During the month of treatment, mean weight increased by 2.97 kg (P=0.01) (Table 1), despite increasing the frusemide dosage in four patients who developed oedema after one week. Mean weight increased by 1.1 kg (P=0.01) even in the 9 patients who did not become oedematous.

RENAL AND HEMODYNAMIC EFFECTS

In the control period the patients were normotensive, but had elevated total systemic vascular resistance and reduced cardiac output (Table 2). Both captopril and prazosin reduced total systemic vascular resistance at one month (Fig. 1); but only captopril reduced mean blood pressure. Neither drug increased cardiac output significantly.

The control glomerular filtration rate and renal blood flow were reduced, the filtration fraction was normal (Table 2). After one month, glomerular filtration rate was not altered by either treatment.

Despite the greater fall in blood pressure during captopril treatment, renal blood flow increased at one month (Fig. 2). Together with the fall in systemic vascular resistance there was a reduction in renal vascular resistance, and although total cardiac output did not increase there was an increase in the percentage of the cardiac output reaching the kidneys (Fig. 3), indicating that there had been preferential redistribution of blood flow to the kidneys. The filtration fraction fell slightly, since glomerular filtration rate was unchanged despite an increase in renal plasma flow (Table 2).

Although total systemic vascular resistance was also reduced by prazosin, renal vascular resistance increased, and both renal blood flow and the percentage cardiac output to the kidneys fell (Figs 2, 3), indicating that blood flow had been redistributed away from the kidneys, into other vascular beds. Filtration fraction did not change significantly during prazosin treatment.

The changes in renal blood flow during captopril and prazosin treatment correlated inversely with...
Table 2 Renal and haemodynamic results: Control renal and haemodynamic values, and absolute changes after one month of captopril and prazosin, in 15 patients. [mean (95% confidence limits)]

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Captopril</th>
<th>Prazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml min⁻¹)</td>
<td>53 (45, 62)</td>
<td>-5 (-11, +1)</td>
<td>+3 (-1, +6)</td>
</tr>
<tr>
<td>RBF (ml min⁻¹)</td>
<td>649 (563, 734)</td>
<td>+76* (-158, -21)</td>
<td>-89*</td>
</tr>
<tr>
<td>FF (%)</td>
<td>15 (13, 16)</td>
<td>-3** (-1, -5)</td>
<td>+1 (0.2)</td>
</tr>
<tr>
<td>RVR (dynes cm⁻⁵)</td>
<td>10823 (9250, 12369)</td>
<td>-2738** (+834, +3430)</td>
<td>+2132**</td>
</tr>
<tr>
<td>SVR (dynes cm⁻⁵)</td>
<td>1870 (1575, 2166)</td>
<td>-261* (-521, -1)</td>
<td>-149* (-298, -1)</td>
</tr>
<tr>
<td>CO (l min⁻¹)</td>
<td>3.6 (3.1, 4.1)</td>
<td>+0.1 (-0.6, +0.8)</td>
<td>+0.4 (-0.1, +0.9)</td>
</tr>
<tr>
<td>% CO to kidneys</td>
<td>19 (16, 22)</td>
<td>+2.5** (+0.8, +4.0)</td>
<td>-5** (-8, -2)</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>83 (79, 88)</td>
<td>-9** (-15, -4)</td>
<td>-4 (-9, +1)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01.

RBF — renal blood flow
GFR — glomerular filtration rate
FF — filtration fraction
RVR — renal vascular resistance
SVR — systemic vascular resistance
CO — cardiac output
BP — blood pressure
N — normal values

Figure 1 Haemodynamic changes after one month of captopril and prazosin, in 15 patients. The mean control value is given (95% confidence limits), and then the absolute changes shown, with 95% confidence bar, for total systemic vascular resistance (SVR), mean blood pressure (BP) and cardiac output.

the corresponding changes in body weight at one month (r= -0.53 P=0.003); those patients in whom renal blood flow decreased on treatment tended to gain weight, those in whom renal blood flow increased tended to lose weight.

NEUROENDOCRINE EFFECTS

The control resting plasma renin activity, aldosterone and noradrenaline were elevated (Table 1). Inhibition of angiotensin converting enzyme with captopril reduced plasma aldosterone...
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and increased plasma renin activity, both at one week and one month (Table 1). The increase in renal blood flow after one month of captopril treatment correlated with the control plasma renin activity (Fig. 4): patients who initially had greater activation of their renin–angiotensin systems had greater increases in renal blood flow during captopril treatment.

Inhibition of the alpha adrenergic sympathetic system with prazosin increased resting plasma aldosterone at one week (Table 1). After one month, when fluid retention and circulatory expansion had occurred, plasma renin activity and aldosterone remained abnormally elevated, similar to control values.

The changes in plasma aldosterone after one week's treatment with captopril and with prazosin correlated with the changes in body weight after one month ($r=0.48$, $P=0.007$): increasing aldosterone was associated with subsequent weight gain, decreasing aldosterone with weight loss.

Plasma noradrenaline increased during prazosin treatment, but tended to fall during captopril treatment. The six patients who became oedematous during prazosin treatment had greater increases in plasma noradrenaline at one month ($+539\, \text{pg}\, \text{ml}^{-1}$) than those who did not become oedematous ($+5\, \text{pg}\, \text{ml}^{-1}$, unpaired $t=2.53$, $P=0.03$).

BIOCHEMICAL EFFECTS

The control mean plasma sodium was $136\, \text{mmol}\, \text{l}^{-1}$ ($134, 138$), and the control mean urinary sodium excretion was $120\, \text{mmol}\, \text{per 24 h}\, (86, 154)$; neither variable changed during the study. Mean plasma potassium increased during captopril treatment.

Figure 2. Renal changes after one month of captopril and prazosin, in 15 patients. The mean control value is given (95% confidence limits), and then the absolute changes shown, with 95% confidence bar, for glomerular filtration rate (GFR) and renal blood flow (RBF).

Figure 3. Renal changes after one month of captopril and prazosin, in 15 patients. The mean control value is given (95% confidence limits), and then the absolute changes shown, with 95% confidence bar, for renal vascular resistance (RVR) and the % cardiac output (CO) to the kidneys.

Figure 4. Relationship between control plasma renin activity (PRA) and changes in renal blood flow (RBF) after one month of captopril, in 15 patients.
from a control value of 3.8 mmol l\(^{-1}\) (3.6, 4.0) to 4.1 (3.9, 4.3) (\(P=0.03\)); prazosin did not alter plasma potassium. The control blood urea was slightly elevated at 9.9 mmol l\(^{-1}\) (8.1, 11.6); control plasma creatinine was normal, 119 \(\mu\)mol l\(^{-1}\) (107, 131). Blood urea did not change during captopril treatment, but during prazosin treatment it fell to 8.0 mmol l\(^{-1}\) (6.3, 9.7) (\(P=0.01\)). Mean plasma creatinine did not change significantly during either treatment period, but we noted slight increases (up to 34 \(\mu\)mol l\(^{-1}\)) in four patients after one week of captopril treatment, which returned to normal with continued treatment at one month.

PLASMA PRAZOSIN CONCENTRATIONS

After one month's treatment, mean plasma prazosin concentration was 29.2 ng ml\(^{-1}\) (18, 41) before a maintenance dose, increasing to 40.4 (29, 52 paired \(t=2.87, P=0.02\)) two hours after a 4 mg maintenance dose. These drug levels are high, despite the relatively low dose of prazosin used, and could have resulted in inhibition of pre-synaptic alpha\(_2\) adrenoceptors, in addition to the expected inhibition of post-synaptic alpha\(_1\) adrenoceptors.

Discussion

In chronic heart failure, renal blood flow is reduced not only because of the reduction in cardiac output but also because of specific renal vasoconstriction\[^3,4\] As arterial pressure falls, baroreceptor reflexes stimulate sympathetic activity. Renal sympathetic nerves terminate on juxtaglomerular cells of afferent arterioles; sympathetic stimulation causes afferent arteriolar vasoconstriction and facilitates renin release from the adjacent macula densa cells. Reduction in renal perfusion pressure is the main stimulus for renin release\[^6\], leading to formation of angiotensin II within the kidney\[^20\] as well as systemically. Although the systemic effects of angiotensin II are widespread, including systemic vasoconstriction and hyperaldosteronism, the intra-renal effects of the renin–angiotensin system are also important in circulatory homeostasis and renal autoregulation.

If renal perfusion and renal blood flow are reduced gradually, glomerular filtration rate remains near normal. This maintenance ('autoregulation') of glomerular filtration rate is due to vasoconstriction of efferent arterioles, distal to the glomeruli, and is mediated by angiotensin II\[^20,21\]. In addition to its role in maintaining glomerular filtration rate, angiotensin II has other renal actions which facilitate sodium and water retention. Post-glomerular vasoconstriction of autoregulatory cortical nephrons reduces peritubular hydrostatic pressure, encouraging reabsorption of renal interstitial fluid, and also results in intra-renal blood flow redistribution toward juxtamedullary nephrons, which have a greater salt-retaining capability\[^4\]. Angiotensin II also has direct cellular actions, increasing tubular reabsorption of sodium, and causing glomerular mesangial cell contraction which might reduce glomerular filtration rate\[^21\].

In early or mild heart failure, then, the intra-renal renin-angiotensin system, facilitated by sympathetic activation, maintains renal function and provides homeostatic circulatory support. In more advanced heart failure however, as cardiac output, renal perfusion pressure and renal blood flow decrease progressively, glomerular filtration rate can no longer be maintained just by efferent arteriolar vasoconstriction. Increasing activation of the renin-angiotensin and sympathetic systems causes profound and widespread renal and systemic vasoconstriction and fluid retention, which by increasing left ventricular afterload becomes an inappropriate and harmful response in chronic heart failure\[^6-7\].

Inhibition of sympathetic alpha adrenoceptors and of the renin–angiotensin system might be expected to result in renal vasodilatation in patients with heart failure, but such interruption of homeostatic reflexes would only be beneficial if renal perfusion also improved at the same time. If, for example, efferent arteriolar vasodilatation occurs without any increase in renal perfusion then glomerular filtration rate would fall.

Studies of renal blood flow and function after neuroendocrine inhibition have been performed, though only in patients with severe heart failure, and have provided variable results. After inhibition of the alpha adrenergic sympathetic system with prazosin, renal blood flow did not increase despite an increase in cardiac output\[^21\]. Inhibition of the renin–angiotensin system with captopril has been reported to cause an acute increase in renal blood flow\[^23,24\], but acute reductions in renal perfusion and function have also been reported\[^25,26\], correlating with the acute reduction in arterial pressure. Even if renal perfusion is reduced acutely by inhibition of the renin–angiotensin system, continued treatment is associated with a sustained increase in renal perfusion and function\[^26\], indicating that some intra-renal changes can occur slowly to allow improved renal function even at reduced arterial...
pressure. In a placebo controlled double-blind study, renal perfusion increased with long-term captopril treatment.

We report the first study that has evaluated the long-term renal, haemodynamic, hormonal and clinical responses to specific neuroendocrine inhibition in patients with moderate chronic heart failure, in a double-blind cross-over comparison of the effects of captopril and prazosin. We studied only stable patients with moderate heart failure (NYHA class II–III) since in more severely ill patients the renal and hormonal changes that occur with treatment may be less important determinants of clinical response than the natural history of the underlying disease itself.

Measurements were made simultaneously of central haemodynamic variables, glomerular filtration rate, renal plasma flow and plasma renin activity, aldosterone and noradrenaline, thereby allowing a detailed analysis of the interrelationships between these factors. From measured variables we have derived systemic and renal vascular resistances and the percentage of total cardiac output which perfuses the kidneys. Such derived values must be interpreted cautiously, as they are prone to greater error than original measurements. Nevertheless, we find analysis of the changes in these derived values to be useful, and when assessed in association with the other results the overall trend in circulatory change is appreciated more clearly.

Although the patients in this study had only moderate chronic heart failure, the control renal blood flow and the proportion of the total cardiac output perfusing the kidneys was reduced, indicating specific renal vasoconstriction and redistribution of blood flow away from the kidney. Control plasma renin activity, aldosterone and noradrenaline were elevated, indicating activation of the renin–angiotensin and sympathetic systems.

Inhibition of alpha adrenoceptors with prazosin caused systemic but not renal vasodilatation. Prazosin stimulated the renin–angiotensin system and increased plasma noradrenaline, causing renal vasoconstriction and redistribution of blood flow away from the kidney, and resulting in a reduction in renal perfusion and fluid retention. The reduction in renal blood flow during prazosin treatment may have been due primarily to renal vasoconstriction, or to vasodilatation in other vascular beds causing a ‘steal’ phenomenon diverting blood away from the kidneys. Renal vasoconstriction with prazosin could have been due to unopposed reflex activation of the renin–angiotensin system when arterial pressure was reduced by systemic vasodilatation. Additionally, the high plasma concentrations of prazosin may have resulted in inhibition of pre-synaptic α2 adrenoceptors, thereby increasing circulating noradrenaline, and stimulating renal sympathetic adrenoceptors to cause renin release and renal vasoconstriction.

Although sympathetic inhibition with prazosin reduced systemic vascular resistance and thus left ventricular afterload, this did not result in clinical benefit. Our results suggest that lack of clinical improvement with prazosin treatment is related to its adverse renal and hormonal effects.

Inhibition of the renin–angiotensin system with captopril caused systemic vasodilatation and reduction in arterial pressure, but did not increase cardiac output. Despite this, renal blood flow and the proportion of cardiac output to the kidneys increased at one month, indicating that there had been specific renal vasodilatation. These renal changes were associated with sustained reduction in plasma aldosterone, a tendency to reduction in plasma noradrenaline, improved natriuresis and weight loss, and long-term clinical improvement. We found that the greatest improvement in renal blood flow during captopril treatment occurred in the patients who had the highest initial plasma renin activity.

Although renal blood flow increased with captopril, glomerular filtration rate did not increase, and filtration fraction fell, indicating there had been efferent arteriolar vasodilatation. Glomerular filtration rate was maintained during captopril treatment despite a fall in mean arterial pressure of 9 mmHg. Acute changes in renal perfusion were not measured, but we found no clinical and minimal biochemical evidence of deterioration in renal perfusion during the first week of captopril treatment. In fact two patients who had developed oedema on prazosin, despite an increase in diuretic dose, lost this oedema within one week when crossed over to captopril, even though the dose of diuretic was reduced.

Our favourable results with captopril may have been due in part to the patient population having less severe heart failure than patients in previous studies. In more severe heart failure, improvement in renal perfusion may depend more on increasing the severely reduced cardiac output and on maintaining perfusion pressure than on redistributing blood flow to the kidney by specific vasodilatation alone.

This study has shown that the renal and hormonal
abnormalities of patients with moderate chronic heart failure can be improved by inhibition of the renin–angiotensin system, leading to long-term clinical improvement.

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References


