ACUTE AND CHRONIC EFFECTS OF CAPTOPRIL THERAPY IN PATIENTS WITH REFRACTORY HEART FAILURE

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1 The acute and chronic effects of the oral converting-enzyme inhibitor captopril were studied in 10 patients with refractory heart failure. Nine patients were in New York Heart Association functional class IV and one in class III. The acute haemodynamic and humoral effects were measured after the administration of 25–50 mg captopril.

2 Oral captopril reduced mean heart rate from 82 ± 13 (SD) to 76 ± 13 ($p < 0.01$), mean arterial pressure from 78 ± 8 to 61 ± 7 mm Hg ($p < 0.01$), mean pulmonary capillary wedge pressure from 29 ± 3 to 17 ± 4 mm Hg ($p < 0.01$), and systemic vascular resistance from 1667 ± 274 to 968 ± 152 dyne/s/cm⁻⁵ ($p < 0.01$). Cardiac index increased from 1.7 ± 0.2 to 2.5 ± 0.6 l/min/m² ($p < 0.01$) and stroke volume index 22 ± 4 to 32 ± 7 ml/m² ($p < 0.01$). Angiotensin II fell from a control of 85 ± 45 pg/ml to 27 ± 14 pg/ml ($p < 0.01$) measured at peak effect of captopril.

3 Captopril 25–50 mg every eight hours was continued long term. At mean follow-up 8 ± 5 months (maximum 17 months) seven patients had improved to NYHA functional class III and three to functional class II. Six of the 10 patients died, four suddenly. The one-year actuarial survival was 30%.

4 Haemodynamic and humoral effects were restudied on therapy in six patients after at least 6 months' treatment and their results compared with those in the short-term study. In the late study captopril reduced mean heart rate from 76 ± 7 to 71 ± 8 ($p < 0.05$), mean arterial pressure from 81 ± 4 to 72 ± 6 mm Hg ($p < 0.05$), pulmonary capillary wedge pressure from 27 ± 5 to 19 ± 2 ($p < 0.05$), systemic vascular resistance from 1812 ± 445 to 1234 ± 244 dyne/s/cm⁻⁵ ($p < 0.05$). Cardiac index increased from 1.9 ± 0.2 to 2.4 ± 0.2 l/min/m² and stroke volume index from 25 ± 4 to 35 ± 6 ml/m². There was no significant difference between the peak haemodynamic effect of captopril or the percentage change from control measured in the acute or the late study for the six patients. The acute reduction in angiotensin II concentrations was maintained at 6 months with a mean value of 5 ± 6 pg/ml. Mean plasma aldosterone concentration was reduced from 1412 ± 704 pmol/l before treatment to a mean of 387 ± 85 pmol/l at the 6 month study.

5 It is concluded that vasodilator therapy with captopril produces a beneficial acute clinical and haemodynamic response which is sustained at follow-up and that despite symptomatic and objective improvement in these patients with refractory heart failure survival remains poor.

Introduction

The importance of afterload as a major determinant of ventricular performance has stimulated the development and clinical application of several vasodilator drugs for the management of patients with congestive heart failure (Franciosa, 1982; Walsh & Greenberg, 1981). Most clinical experience has been obtained with the blocking agent prazosin and the combination of hydralazine and nitrates, but widespread clinical use of these drugs has been limited by the development of side effects and pharmacodynamic tachyphylaxis (Packer *et al.*, 1979).

Converting-enzyme inhibition represents a novel approach to afterload reduction since it specifically inhibits the angiotensin-mediated regional vasoconstriction known to be an important mechanism in the

raised systemic vascular resistance characteristic of congestive heart failure (Cohn, 1973). Short-term studies have now shown that captopril, the first oral converting-enzyme inhibitor clinically available, is a powerful vasodilatory agent producing beneficial haemodynamic effects in most patients with chronic heart failure, but the long-term results of captopril therapy remain uncertain (Ader *et al.*, 1980; Davis *et al.*, 1979; Dzau *et al.*, 1980).

Methods

We have studied the short- and long-term clinical and haemodynamic effects of oral captopril in 10 patients

Table 1 Clinical characteristics of study population

Case No.	Age/ sex	Diagnosis	NYHA class	Ejection fraction	Previous therapy	
					Diuretics (mg)	Vasodilators (mg)
1	50 M	IHD	IV	0.23	Frus 240	Isd 40
2	65 M	IHD	IV	0.11	Eth 150	Hyd 150
3	59 M	COCM	IV	0.21	Mod 10	Hyd 300
4	57 M	IHD	IV	0.13	Frus 500	Praz 2 Isd 80
5	58 M	IHD	IV	0.15	Frus 80	Hyd 150
6	55 M	IHD	IV	0.32	Frus 1500	Praz 15 Isd 300
7	60 M	IHD	III	0.35	Frus 80	Praz 4 Isd 30
8	61 M	IHD	IV	0.32	Frus 240	Hyd 300
9	70 M	COCM	IV	0.19	Frus 1250	Hyd 300 Isd 80
10	57 M	IHD	IV	0.24	Frus 320	Isd 80
Mean	59			0.25		
± SD	± 6			± 0.11		

IHD = ischaemic heart disease; COCM = congestive cardiomyopathy. Frus = frusemide; Eth = ethacrynic acid; Mod = Moduretic; Isd = isosorbide dinitrate; Hyd = hydralazine; praz = prazosin.

with stable chronic refractory congestive heart failure. The clinical characteristics of the 10 patients are shown in Table 1. Nine patients were in New York Heart Association functional class IV and one in functional class III. The aetiology of their heart failure was ischaemic heart disease in seven and congestive cardiomyopathy in three. The mean resting left ventricular ejection fraction, determined by radionuclide techniques was 0.25 ± 0.11 (SD). All 10 patients had received previous unsuccessful trials of other vasodilator drugs: five had received hydralazine (mean dose 300 mg daily), six long-acting nitrates (mean dose 53 mg daily), and three prazosin (mean dose 14 mg daily). Informed consent was obtained in all cases.

Before determining the initial haemodynamic study baseline we measured plasma renin activity, angiotensin II, aldosterone, and 24-hour urinary sodium excretion. Oral vasodilatory drugs were stopped at least 24 hours before the study and diuretics were withheld during the acute haemodynamic study. Initial right heart catheterisation was performed in all 10 patients using a triple-lumen balloon-tipped thermodilution catheter to obtain control pressures and cardiac output. After an oral dose of 25–50 mg captopril haemodynamic variables and cardiac output were measured at 30-minute intervals for the first three hours. Haemodynamic monitoring was then continued for at least 24 hours while patients were stabilised with 25–50 mg captopril given every eight hours. Cardiac index, stroke volume index, stroke work index, and systemic vascular resistance were calculated from the data collected from each patient.

After discharge patients were followed at frequent intervals and their clinical and humoral status assessed. Six of the 10 patients underwent a second haemodynamic study at a mean of 7 months (range 6–9) after

the start of captopril treatment. Right heart catheterisation was performed as in the initial study and haemodynamic measurements made immediately before the usual dose of captopril and for three hours afterwards without interruption of maintenance therapy. Plasma renin, angiotensin II, aldosterone, and 24-hour urinary sodium excretion were again measured.

Statistical analysis was performed using Student's paired *t* test with two-tailed distribution. The study protocol was approved by the ethics committee of the Prince Henry and Prince of Wales Hospitals.

Results

Initial haemodynamic study

The results of the acute haemodynamic study for the 10 patients are shown in Table 2. Oral captopril produced a small reduction in mean heart rate from 82 to 78 ($p < 0.01$). Mean arterial pressure fell approximately 17% from 78 to 61 mm Hg ($p < 0.01$). Mean right atrial pressure for the patient group fell from 13 to 9 mm Hg ($p < 0.01$), pulmonary artery pressure from 41 to 30 mm Hg ($p < 0.01$) and pulmonary capillary wedge pressure from 29 to 17 mm Hg ($p < 0.01$). Mean cardiac index increased from 1.7 to 2.5 l/min/m² ($p < 0.01$), stroke volume index from 22 to 32 ml/m² ($p < 0.01$), and stroke work index from 18 to 25 g.m/m². Captopril produced a substantial reduction (approximately 40%) in calculated systemic vascular resistance from a mean of 1667 to 968 dyne/s/cm⁻⁵ ($p < 0.01$). The control haemodynamics were measured to determine whether any of these variables were predictive of the magnitude of the acute haemodynamic response to captopril.

Table 2 Acute haemodynamic effects of captopril

Case No.	Heart rate	Mean arterial pressure	Right arterial pressure	Pulmonary artery pressure	Pulmonary wedge pressure	Cardiac index	Stroke volume index	Stroke work index	Systemic vascular resistance
1	Control 74	80	12	43	31	1.5	20	15	1754
	50 mg 70	63	5	20	19	2.0	28	24	1148
2	Control 102	90	9	38	30	1.4	19	16	2160
	25 mg 99	53	4	24	14	3.2	32	28	784
3	Control 101	70	15	34	25	1.6	16	12	1701
	25 mg 90	62	13	33	16	2.1	23	18	1170
4	Control 91	65	9	36	30	1.7	18	14	1553
	50 mg 87	58	12	30	22	2.3	26	18	893
5	Control 82	85	12	45	28	2.0	25	24	1850
	25 mg 80	73	12	35	20	3.9	48	46	827
6	Control 88	86	16	38	26	2.0	23	22	1293
	50 mg 87	72	17	35	18	2.4	27	22	1002
7	Control 61	66	10	40	25	1.9	31	20	1244
	25 mg 60	56	6	35	17	2.3	39	22	1000
8	Control 70	80	18	52	36	1.5	21	16	1922
	50 mg 64	66	11	36	22	2.4	38	26	700
9	Control 70	80	16	42	28	1.6	23	20	1766
	25 mg 60	53	8	27	12	1.9	32	22	1090
10	Control 82	73	12	46	26	1.7	20	16	1422
	25 mg 78	58	1	25	8	2.2	28	23	1070
Mean control	82 ± 13	78 ± 8	13 ± 3	41 ± 5	29 ± 3	1.7 ± 0.2	22 ± 4	18 ± 4	1667 ± 274
Mean peak	78 ± 13**	61 ± 7**	9 ± 5*	30 ± 5**	17 ± 4**	2.5 ± 0.6**	32 ± 7**	25 ± 8**	968 ± 152**

* $p < 0.05$; ** $p < 0.01$.

The baseline systemic vascular resistance was predictive for the group as shown by a significant correlation with the magnitude of change in cardiac index ($r = 0.7$; $p = 0.013$), stroke volume index ($r = 0.6$; $p = 0.05$), and stroke work index ($r = 0.6$, $p = 0.05$).

Clinical follow-up

All 10 patients were discharged from hospital receiving 25–50 mg captopril every eight hours. At mean follow-up of 8 ± 5 months (maximum 17 months) seven patients had improved to New York Heart Association class III and three to class II. All patients reported a definite improvement in their exercise tolerance and wellbeing with captopril therapy, and no patient had to discontinue therapy because of drug side effects. Two patients had their dose reduced because of symptoms of orthostatic hypotension on the discharge dose of captopril. The mean daily dose of frusemide required fell from an initial dose of 317 ± 402 mg to 158 ± 227 mg ($p = 0.05$). Associated with the decreased diuretic dosage mean body weight fell from 66 ± 9 to 64 ± 10 kg.

Six of the 10 patients died on follow-up, with the 1-year actuarial survival for the group being 30%. Four of these six patients died suddenly: at two weeks, six weeks, six months, and seven months after beginning treatment despite showing a beneficial symptomatic response to captopril. One other patient (case 9) has had two separate episodes of ventricular fibrillation, from which he has been successfully resuscitated and he currently has stable class III dyspnoea. The remaining two patients died of low output failure after progression of their underlying disease after 10 and 11 months of drug treatment.

Late haemodynamic study

Six of the 10 patients were restudied at a mean of 6 months (range 6–9 months) and the results are shown in Table 3 and Figures 1 and 2. In the late study

haemodynamic measurements were taken immediately before the dose of captopril was given and at the peak effect of the drug. Captopril reduced mean heart rate from 76 to 71 ($p < 0.05$), mean arterial pressure from 81 to 72 mm Hg ($p < 0.05$), right atrial pressure from 8 to 5 mm Hg ($p < 0.05$), and mean pulmonary capillary wedge pressure from 27 to 19 mm Hg ($p < 0.05$). Cardiac index increased from 1.9 to 2.4 l/min/m² ($p < 0.05$), stroke volume index from 25 to 36 ml/m² ($p < 0.08$), and stroke work index from 22 to 30 g.m/m² ($p < 0.05$). Captopril produced a 30% reduction in systemic vascular resistance for this group, from 1812 to 1234 dyne/s/cm⁻⁵ ($p < 0.05$). There were no significant differences between the peak haemodynamic effect of captopril measured at the initial and the late study for each of the nine variables examined.

Humoral studies

Baseline humoral studies showed a wide variability of plasma renin activity and angiotensin II concentrations in the 10 patients. The mean plasma renin activity was 20 ± 10 ng/ml/h (range 5–38) and the mean angiotensin II concentration was 85 ± 45 pg/ml (range 11–128). Nine of the 10 patients, however, had raised angiotensin II concentrations and five had levels greater than 100 pg/ml. Plasma angiotensin II measured 90 minutes after the administration of captopril in the initial study fell substantially to 27 ± 14 pg/ml ($p < 0.01$). This low level of angiotensin II was maintained on long-term follow-up, with the mean value at 3 months being 16 ± 9 pg/ml and at the late study 5 ± 6 pg/ml. Baseline plasma renin activity and angiotensin II levels were examined to determine whether any of these variables were predictive of the acute haemodynamic response to captopril. There was no statistically significant correlation between the control level or the magnitude of change of these humoral factors and the acute response to captopril.

Table 3 Haemodynamic measurements after initiation of captopril (acute) and after 6 months of long-term therapy in six patients

	Control	Acute†	Long-term†
Heart rate	73 $\pm$ 8	69 $\pm$ 9*	71 $\pm$ 8
Mean arterial pressure	76 $\pm$ 7	63 $\pm$ 8*	72 $\pm$ 6
Right arterial pressure	13 $\pm$ 3	7 $\pm$ 4*	5 $\pm$ 2
Pulmonary artery pressure	45 $\pm$ 4	30 $\pm$ 7*	35 $\pm$ 6
Pulmonary capillary wedge pressure	29 $\pm$ 4	17 $\pm$ 5*	19 $\pm$ 2
Cardiac index	1.7 $\pm$ 0.2	2.5 $\pm$ 0.7*	2.4 $\pm$ 0.2
Stroke volume index	23 $\pm$ 4	36 $\pm$ 8*	35 $\pm$ 6
Stroke work index	19 $\pm$ 3	27 $\pm$ 9*	30 $\pm$ 5
Systemic vascular resistance	1660 $\pm$ 266	1040 $\pm$ 116*	1234 $\pm$ 244

* $p < 0.05$. † Measured at peak effect of captopril.

Figure 1 Mean cardiac index and pulmonary capillary wedge pressure for the six patients measured in the initial acute study and in the late (six month) study. The immediate significant increase in cardiac index and fall in pulmonary capillary wedge was maintained with long-term captopril therapy. C = control.

Figure 2 Mean stroke volume index and systemic vascular resistance for the six patients measured in the initial acute study and in the late (6-month) study. Note sustained increase in stroke volume index and reduction in systemic vascular resistance with long-term therapy.

The mean control plasma aldosterone for the 10 patients was 1412 ± 704 pmol/l, and after captopril therapy this fell substantially to 387 ± 85 pmol/l after the same study. This reduction in aldosterone was maintained on follow-up, with the six patients in the late study having a mean value of 407 ± 120 pmol/l (Figure 3).

After the start of captopril therapy 24-hour urinary sodium excretion increased from a control value of 27 ± 19 to 108 ± 25 mmol/l 24 h after 3 days of treatment. Despite a significant reduction in requirements for diuretic dosage, urinary sodium excretion remained increased at 128 mmol/24 h when measured at the late study.

Discussion

The results of this study shows that captopril is a potent vasodilator drug which produces beneficial acute and sustained long-term clinical and haemodynamic effects in patients with severe chronic heart failure, even in those patients who have failed on other vasodilator drugs. The results of our initial haemodynamic study are similar to those reported by other groups (Ader *et al.*, 1980; Davis *et al.*, 1979; Dzau *et al.*, 1980). Captopril acts as a balanced vasodilator, dilating both arteriolar resistance vessels as well as venous capacitance vessels. The reduction in ventricular filling pressures and the improvement in cardiac output at rest were associated with improvements in the symptoms of dyspnoea and fatigue in all patients.

The late haemodynamic study showed a continued effect of captopril in our patients, with no evidence of tachyphylaxis. The magnitude of change in the

haemodynamic variables produced by captopril was similar for both the initial and the late study. This is a contrast to long-term experience with other vasodilator drugs, such as prazosin and hydralazine, where tachyphylaxis has been well documented, particularly when endogenous neurohumoral responses have been stimulated (Packer *et al.*, 1979, 1982). Since increased catecholamine and renin-angiotensin activity would tend to oppose long-term vasodilation, inhibition of these neurohumoral responses by captopril may be important in preventing the occurrence of drug tolerance and hence clinical failure (Packer & LeJemtel, 1982).

Since captopril acts as a converting-enzyme inhibitor it might be expected that patients with a high degree of activity of the renin-angiotensin-aldosterone system would be particularly responsive to this unique form of vasodilator therapy. Our study and others have, however, failed to show any relationship between baseline humoral status and captopril response, indicating that the mode of action of this drug is more complex than just a direct effect on reducing concentrations of the vasopressor angiotensin II (Ader *et al.*, 1980; Davis *et al.*, 1979). The relatively few patients in our study also makes this relationship more difficult to establish. The long-term humoral data showed that the inhibition of the renin-angiotensin-aldosterone system is maintained, with no evidence of a 'break-through' phenomenon occurring with long-term treatment. The sustained reduction in aldosterone concentrations was associated with both lower requirements for diuretics in most of our patients and the lack of clinical problems with increased fluid retention. The latter is a not infrequent late side effect of other vasodilator drugs and has also been incriminated in the development of

Figure 3 Effects of captopril on plasma renin activity, angiotensin II, and plasma aldosterone measured at control and after three and six months' treatment. Although there was no significant change in plasma renin activity with captopril therapy, angiotensin II and aldosterone fell to low concentrations, which were maintained on follow-up.

drug tolerance to these agents (Packer *et al.*, 1979).

Our data point to the high mortality of chronic refractory heart failure irrespective of the patients' response to captopril therapy. Other vasodilator studies have also shown a high mortality in patients with severe heart failure and have shown that a major determinant of long-term prognosis is the baseline haemodynamic status (Walsh *et al.*, 1981; Massie *et al.*, 1981). In general, patients with the most advanced myocardial dysfunction have been shown to have the worst prognosis, which raises the possibility that improved long-term results with vasodilator therapy might be obtained if these drugs were used in patients with less severe heart failure—for example NYHA functional class II.

Of interest in our patients with chronic heart failure was the relatively high incidence of sudden deaths. This event occurred in patients who had shown good clinical and even late haemodynamic response to captopril. Ventricular arrhythmias are common in patients with advanced heart failure and presumably were responsible for the sudden deaths in our patients (Franciosa, 1982). This observation has implications for hopes of an improved prognosis with vasodilator therapy since it suggests that in these patients with severe heart failure the occurrence of serious ventricular arrhythmia is an additional important deter-

minant of long-term survival. Perhaps combined long-term vasodilator and antiarrhythmic therapy may be a more useful therapeutic approach in the management of these severely compromised patients.

Captopril was well tolerated by our patient group, with the only problems observed being mild orthostatic hypotension. This is related to the high potency of captopril and was alleviated by reducing the dosage. Increased proteinuria or neutropenia did not occur, and transient rashes were not troublesome. The lack of toxicity in patients with heart failure is probably due to the lower doses required compared with those used in the treatment of patients with hypertension.

In summary, vasodilator therapy with oral captopril produced a beneficial acute clinical and haemodynamic response which was sustained at long-term follow-up. Despite subjective and objective improvement in the severity of congestive heart failure, however, survival in these patients remained poor.

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