ACUTE AND LONG-TERM EFFECTS OF CAPTOPRIL ON EXERCISE CARDIAC PERFORMANCE AND EXERCISE CAPACITY IN CONGESTIVE HEART FAILURE

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1 Although in many studies patients in heart failure treated with captopril have shown acute haemodynamic improvement at rest, little information is available about the haemodynamic response to captopril during exercise or about its effect on exercise tolerance.

2 Haemodynamic measurements were taken at rest and during upright bicycle exercise before and during the first two days of captopril treatment in 15 patients with stable congestive heart failure. At rest, the heart rate and mean arterial pressure both declined (84 ± 11 to 78 ± 7 beats/min ($p < 0.25$) and 85 ± 9 to 64 ± 8 torr ($p < 0.001$), the left ventricular filling pressure dropped dramatically (26 ± 9 to 15 ± 7 torr ($p < 0.001$) while cardiac and stroke indices rose (2.0 ± 0.5 to 2.5 ± 0.6 l/min/m² ($p < 0.001$) and 25 ± 8 to 33 ± 7 ml/min² ($p < 0.001$). Similar directional changes occurred during exercise, with heart rate, mean arterial pressure, and left ventricular filling pressure at maximum exercise all falling (123 ± 15 to 115 ± 16 beats/min ($p < 0.01$); 93 ± 17 to 86 ± 14 torr ($p < 0.05$); and 35 ± 10 to 30 ± 11 torr ($p < 0.001$) respectively). Maximum cardiac index rose slightly, from 3.6 ± 0.7 to 3.9 ± 0.6 l/min/m², acutely, but the change was not significant.

3 Six patients studied taking captopril long term underwent elective recatheterisation after 3 months. In these, either the beneficial haemodynamic changes seen with short-term treatment persisted or further improvement was noted, both at rest and during exercise. Most impressively, maximum exercise index rose from 3.6 ± 0.7 to 4.6 ± 1.0 l/min/m² ($p < 0.05$) and this was associated with an increase in exercise duration (8.0 ± 2.2 to 11.5 ± 1.4 minutes ($p < 0.05$), exercise work load (332 ± 32 to 468 ± 52 kilopond-metres min, ($p < 0.05$) and maximum oxygen consumption (11.8 ± 2.6 to 15.6 ± 2.7 ml/min/kg, ($p < 0.05$). These findings indicate that captopril is beneficial during activity as well as at rest and that chronic treatment increases exercise capacity.

Introduction

Oral vasodilators are now widely used in the treatment of chronic congestive heart failure. Directly acting dilators of vascular smooth muscle, such as hydralazine, minoxidil, the various nitrate preparations, and α -adrenergic antagonists, such as prazosin and trimazosin, have been used alone and in combination to achieve improved cardiac performance (Franciosa *et al.*, 1974; Chatterjee *et al.*, 1976; Taylor *et al.*, 1976; Franciosa *et al.*, 1977; Massie *et al.*, 1977; Miller *et al.*, 1977; Franciosa & Cohn, 1978; Fitchett *et al.*, 1979; Chatterjee *et al.*, 1980; Franciosa *et al.*, 1980; Awan *et al.*, 1981a; Feldman *et al.*, 1981; Franciosa & Cohn, 1981; Massie *et al.*, 1981). In several recent studies captopril, an angiotensin-converting-enzyme inhibitor, produces

acute haemodynamic improvement in patients with chronic congestive heart failure. In a few patients, follow-up measurements have shown that this beneficial effect has been maintained during chronic treatment (Davis *et al.*, 1979; Tarazi *et al.*, 1979; Ader *et al.*, 1980; Levine *et al.*, 1980; Awan *et al.*, 1981b; Dzau *et al.*, 1980; Faxon *et al.*, 1981; Awan *et al.*, 1982).

Most of this information has been collected in severely symptomatic patients during bed rest. Fewer data are available in ambulatory patients whose symptoms occur mainly with activity. We therefore designed the present study to determine the acute and chronic haemodynamic effects of captopril during exercise in a group of relatively stable outpatients.

We also sought to examine the relationship between the haemodynamic findings and measurements of exercise capacity.

Methods

Patients

Fifteen male outpatients with chronic congestive heart failure were entered into the study after giving informed consent. Their mean age was 60 (range 48–72). Symptoms of heart failure had been present for a mean of 37 months (range three months–eight years). Three patients were in New York Heart Association (NYHA) class II, 10 in class III, and two had occasional symptoms during sedentary activity and were therefore considered to be in class IV at the time of the study. The aetiology of heart failure was coronary artery disease in 10 patients, coronary artery disease with hypertension in two, idiopathic cardiomyopathy in two, and rheumatic heart disease after mitral valve replacement in one. One patient had minimal aortic regurgitation, and eight had auscultatory evidence of secondary mitral regurgitation.

All subjects were taking stable doses of digoxin and diuretics at least two weeks before entry into the study. Vasodilators were withdrawn at least four weeks before entry in the three patients who were previously taking them. To qualify for inclusion, patients had to be able to exercise on an upright bicycle for at least three minutes at a workload of 200 kilopond-meters/min. To ensure an exercise end point consistent with heart failure (dyspnoea or fatigue), patients with exercise-limiting angina, claudication, or pulmonary disease (as judged by a forced expiratory volume in one second or a forced expiratory volume: forced vital capacity ratio 70% of predicted) were excluded.

Study protocol

Patients were admitted to hospital at least 24 hours before the baseline studies to ensure drug and dietary compliance. Digoxin and diuretics were continued and given every evening after completion of all measurements. On the first day patients practised on the upright bicycle ergometer to familiarise themselves with the procedure and to estimate their exercise tolerance. The work load was initially set at 200 kilopond-met/minute and was then increased by 100 milopond-met/minute every three minutes. Patients exercised until they developed limiting dyspnoea or fatigue or both.

On day two patients were transferred to the coronary unit, where a balloon-tipped thermodilution catheter was placed in the pulmonary artery percutaneously via the right subclavian vein and a

radial artery was cannulated. To achieve haemodynamic stability patients were then allowed to rest for at least an hour after instrumentation before baseline supine measurements of heart rate, arterial, pulmonary artery, right atrial, and pulmonary capillary wedge pressures. The end-expiratory pulmonary capillary wedge pressure was used as a measure of left ventricular filling pressure except in patients whose pulmonary artery diastolic pressure was substituted for a technically inadequate or unobtainable pulmonary capillary wedge pressure tracing. Cardiac output was determined in triplicate by thermodilution. Exercise was then performed according to the previously described protocol. Heart rate, arterial pressure, and pulmonary artery pressure were measured continuously while right atrial and pulmonary capillary wedge pressures were measured every minute. Cardiac output was determined in triplicate during the final two minutes of the highest work load achieved. Arterial and pulmonary artery blood gases were drawn at rest and at maximal exercise to calculate oxygen consumption. There was no significant difference in duration or work load between the practise and baseline exercises.

On the next morning treatment was begun with captopril 25 mg orally every eight hours. Haemodynamic measurements were taken before dosing, and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after captopril administration. On day 4 of the study the captopril dosage was increased to 50 mg, except in three patients who received 25 mg because of asymptomatic hypotension. Ninety minutes after they had taken captopril supine resting haemodynamic measurements were recorded. Upright exercise was then performed as described above.

Of the 15 patients studied acutely, seven were eventually discharged taking captopril. The captopril dosage was gradually increased to 100 mg three times a day or as close to this target dose as permitted by the blood pressure response. All other medications were maintained at constant doses.

After 3 months, six of these seven patients agreed to undergo elective recatheterisation. On the morning of admission captopril and diuretics were withheld. After a 1-hour stabilisation period after catheter placement, resting haemodynamic measurements were recorded. Patients were then given their doses of captopril, and after 90 minutes resting and exercise haemodynamic measurements were performed. Cardiac output and blood gases were measured both at the pretreatment maximum work load and, if the patient was able to exercise longer, at peak exercise.

Calculations and statistical analysis

The following measurements were derived from the measured haemodynamic variables:

$$\text{Cardiac index (in l/min/m}^2\text{)} = \frac{\text{Cardiac output}}{\text{Body surface area}}$$

$$\text{Stroke index (in ml/m}^2\text{)} = \frac{\text{Cardiac index}}{\text{Heart rate}}$$

$$\text{Systemic vascular resistance (dyne/s/cm}^{-5}\text{)} = \frac{\text{Mean arterial pressure-right arterial pressure}}{\text{Cardiac output}} \times 80$$

$$\text{O}_2 \text{ content (ml/dl)} = \text{O}_2 \text{ saturation} \times \text{haemoglobin concentration} \times 1.34$$

$$\text{O}_2 \text{ consumption (ml/min)} = (\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}) \times \text{Cardiac output}$$

The arterial and mixed venous (pulmonary artery) oxygen saturations were derived from the PO_2 measurements using a standard nomogram.

The significance of the acute vasodilator effect of captopril on haemodynamic measurements and on maximal oxygen consumption was assessed by paired *t* tests. The relationship of acute and chronic effects of captopril on these measurements and on exercise tolerance was analysed using two-way analyses of variance and Neumann-Keuls multiple range tests. All data are presented as the mean $\pm$ 1 standard deviation.

Results

Acute response to captopril at rest

The effect of captopril on resting haemodynamic measurements in the 15 patients studied acutely are illustrated in Figures 1 and 2. After captopril both the 90 minute measurements taken immediately before

exercise and the peak resting response to captopril are shown. Peak drug effect, which was determined by the maximum reduction in blood pressure and systemic vascular resistance, occurred from 0.5 to 6 hours after medication.

At rest there was a modest but significant decrease in heart rate from 84 ± 11 to 78 ± 11 beats/min at 90 minutes ($p < 0.01$) to 78 ± 7 beats/min at peak effect ($p < 0.025$). Mean arterial pressure fell dramatically, from 85 ± 9 to 72 ± 13 mm Hg at 90 minutes ($p < 0.001$) and to 64 ± 3 mm Hg ($p < 0.001$) at peak response. The systolic blood pressure dropped into the 60s in two subjects, but both remained asymptomatic and required no treatment. Similarly, the systemic vascular resistance was reduced from a pre captopril value of 1600 ± 500 to 1430 ± 480 dyne/s/cm⁻⁵ ($p < 0.05$) and further declined to 990 ± 250 dyne/s/cm⁻⁵ at peak drug effect ($p < 0.001$).

Left ventricular filling pressure decreased from 26 ± 9 to 18 ± 9 mm Hg at 90 minutes, and further to 15 ± 7 mm Hg at peak drug effect (both $p < 0.001$), a mean peak reduction of 42%. Cardiac index rose by 25% at peak effect from 2.0 ± 0.5 to 2.5 ± 0.6 l/min/m² ($p < 0.001$). Because of the variable individual time courses of the captopril effect there was, however, no appreciable change for the group as a whole at 90 minutes. The stroke index changed in a similar manner, rising by 32% at peak effect from 25 ± 8 to 33 ± 7 ml/m² ($p < 0.001$) and showing no significant change at 90 minutes.

Acute response to captopril during exercise

The acute haemodynamic effects of captopril during exercise, which were directionally similar to those at

Figure 1 Captopril produced a modest, but significant decrease in heart rate (HR). The reduction in mean blood pressure (MAP) from 85 ± 9 pre-captopril (Pre) to a nadir of 64 ± 8 mm Hg at peak captopril effect (peak) was dramatic and occasionally worrisome, although well tolerated at bed rest. Calculated systemic resistance (SVR) fell concomitantly.

Figure 2 The left ventricular filling pressure fell in all patients, from 26 ± 9 to 15 ± 7 mm Hg at peak effect. The changes in cardiac and stroke indices followed a more variable time course, and achieved statistical significance only when the individual peak responses were grouped together, yielding 25% and 32% increases respectively.

Figure 3 The haemodynamic changes during exercise after captopril were directionally similar to those at rest, but generally less dramatic. Thus, heart rate, mean arterial pressure, and systemic vascular resistance at the same level of exercise all fell modestly.

rest, are shown in Figures 3 and 4. During upright exercise, captopril produced significant haemodynamic improvement at the same level of exercise achieved before treatment. The maximum heart rate decreased from 123 ± 15 to 115 ± 16 bpm ($p < 0.01$), and the mean arterial pressure fell from a pre-captopril level of 93 ± 17 to 86 ± 14 mm Hg ($p < 0.05$) after-captopril. Although exercise lowered the systemic vascular resistance considerably, to 900 ± 174 from a resting value of 1660 ± 500 dyne/s/cm⁻⁵, there was a further reduction during post-captopril exercise to 780 ± 207 dyne/s/cm⁻⁵

($p < 0.01$). The left ventricular filling pressure at the same level of exercise fell from 35 ± 10 to 30 ± 11 mm Hg ($p < 0.001$). The maximum cardiac index rose slightly from 3.6 ± 0.7 to 3.9 ± 0.6 (l/min/m²) but the change was not significant. There was a modest but significant increase in stroke index from 30 ± 5 to 34 ± 8 ml/min/m² ($p < 0.05$).

Chronic haemodynamic responses to captopril

The six patients maintained on captopril who were restudied at 3 months were comparable with the

Figure 4 The left ventricular filling pressure was somewhat lower (35 ± 10 v 31 ± 11 mm Hg) and stroke index rose slightly (30 ± 5 to 34 ± 8 ml/m²) at peak exercises, but exercise cardiac index was not altered acutely.

larger group in age, cause of heart failure, duration of heart failure, functional class, and pretreatment haemodynamic measurements.

Table 1 shows the change in resting haemodynamic measurements after 3 months treatment with captopril. In this smaller group the slight decrease in heart rate seen both acutely and chronically was not significant. The acute decline in mean arterial pressure from 83 ± 9 to 67 ± 6 mm Hg was greatly attenuated at 3 months to 80 ± 12 mm Hg. On the other hand, the acute beneficial effect of captopril on left ventricular filling pressure, a reduction from 25 ± 10 to 16 ± 8 mm Hg, was maintained during long-term therapy. Similarly the increase in cardiac index from 2.1 ± 0.5 to 2.6 ± 0.4 l/min/m² seen acutely persisted at 3 months (2.4 ± 0.5 l/min/m²). Stroke index also was significantly higher during chronic therapy (28 ± 9 v 34 ± 6 ml/m²). The acute decrease in systemic vascular resistance from 1480 ± 260 to 970 ± 210 dyne/s/cm⁻⁵ was somewhat attenuated, but the 3 month systemic vascular resistance (1290 ± 220 dyne/s/cm⁻⁵) was still below the control value.

The long-term response to captopril during exercise in the restudied patients is shown in Figures 5 and 6. Heart rate, which decreased slightly acutely from 122 ± 12 to 111 ± 15 beats/min was not significantly different, 114 ± 23 beats/min, at 3 months. Mean arterial pressure during exercise, which had decreased acutely, returned to the pretreatment level during chronic treatment. Exercise left ventricular filling pressure showed an even greater decrease at 3 months than in the short term, declining from 40 ± 11 to 26 ± 11 mm Hg, ($p < 0.05$). The small acute increase in maximum cardiac index from 3.6 ± 0.7 to 4.0 ± 0.6 l/min/m², achieved significance during long-term treatment, when it rose to 4.6 ± 1.0 l/min/m² ($p < 0.05$). Exercise stroke index also improved further at 3 months to 42 ± 6 ml/m² from the acute treatment value of 26 ± 9 ml/m².

Acute and long-term effects of captopril on exercise tolerance

Figure 7 illustrates the acute and long-term effects of

Table 1 Chronic haemodynamic effect at rest ($n = 6$).

	After captopril		
	Before captopril	Acute	3 mos
Heart rate	77 ± 8	71 ± 10	69 ± 8
Mean arterial pressure	83 ± 9	$67 \pm 6^{**}$	80 ± 12
Left ventricular filling pressure	25 ± 10	$16 \pm 8^{**}$	$16 \pm 7^{**}$
Cardiac index	2.1 ± 0.5	$2.6 \pm 0.4^{**}$	$2.4 \pm 0.5^*$
Stroke index	28 ± 9	$36 \pm 6^{**}$	$34 \pm 7^*$
Systemic vascular resistance	1480 ± 260	$970 \pm 210^{**}$	$1290 \pm 220^*$

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

Figure 5 In this and the next 2 figures, the pre-captopril (Pre), acute captopril (Post), and 3-month captopril (3 Mos) exercise measurements in the six recatheterised patients are shown. Heart rate was not greatly affected, although one patient with known sick sinus syndrome became pacemaker dependent during maintenance captopril. Exercise blood pressure returned toward baseline values.

Figure 6 The small acute reduction in exercise left ventricular filling pressure either persisted or progressed further. Similarly exercise cardiac and stroke index improved further on long-term treatment.

captopril on exercise tolerance. Despite the acute haemodynamic improvement at rest and during exercise, there was no immediate change in exercise duration, work load, or oxygen consumption. In contrast, after 3 months of captopril treatment each of these indices of exercise capacity had improved in every patient.

The mean exercise duration increased by 31% from 8.0 ± 2.2 to 11.5 ± 1.4 minutes at 3 months ($p <$

0.05), with individual increases ranging from 2 to 7.5 minutes. The mean maximum work load increased 332 ± 32 to 468 ± 52 kiloponds-met/min at three months ($p < 0.05$), an improvement of 41%. Maximum oxygen consumption rose by 25% from 11.8 ± 2.6 to 15.6 ± 2.7 ml/min/kg at three months ($p < 0.05$), with the individual increments ranging from 0.9 to 7.9 ml/min/kg. The two patients who showed the greatest improvement in work load and oxygen

Figure 7 All 3 measurements of exercise capacity also improved, including the duration of upright bicycle exercise, the highest work load completed, and calculated maximum oxygen consumption. The values are discussed in the text.

consumption also had the largest increases in cardiac and stroke indexes.

Clinical response during long-term therapy

The clinical response to chronic captopril treatment in the six patients who were electively recatheterised was variable. Although all six patients showed improvement in exercise duration, work load, and oxygen consumption, only two improved by a full New York Heart Association functional class, from classes III and IV respectively. These two patients also exhibited the greatest increases in exercise work load, oxygen consumption and cardiac and stroke indexes. Three patients improved subjectively and increased their exercise tolerance but not sufficiently to warrant a change in New York Heart Association classification. The remaining patient showed no subjective or objective response. The one patient who did not agree to elective recatheterisation improved modestly. Long-term captopril therapy was well tolerated, with only one patient experiencing a mild change in taste and a transient rash, which were thought to be drug-related.

Discussion

Captopril is unique among the currently available oral vasodilating agents in that it specifically inhibits the converting-enzyme responsible for the production of angiotensin II (Peach, 1977). This action interferes with compensatory reflex mechanisms which are

responsible for raising the systemic vascular resistance and increasing sodium and volume retention in patients with chronic congestive heart failure. Inhibition of angiotensin II should result in a fall in systemic vascular resistance and left ventricular afterload with a consequent improvement in cardiac output, and this has been well documented at rest after captopril administration (Davis *et al.*, 1979; Tarazi *et al.*, 1979; Ader *et al.*, 1980; Levine *et al.*, 1980; Awan *et al.*, 1981b; Dzau *et al.*, 1980; Faxon *et al.*, 1981; Awan *et al.*, 1982). Additionally, we and other investigators have shown that captopril has a significant beneficial effect on left ventricular filling pressure that is not adequately explained by its effect on angiotensin II levels (Rose *et al.*, 1962; Davis *et al.*, 1979; Tarazi *et al.*, 1979; Ader *et al.*, 1980; Levine *et al.*, 1980; Awan *et al.*, 1981; Dzau *et al.*, 1980; Awan *et al.*, 1982). The further preload effect may be due to the vasodilator action of bradykinin or prostaglandins (Engel *et al.*, 1972; Dorer *et al.*, 1974) or to an increase in venous capacitance caused by a withdrawal of sympathetic tone after treatment (Zimmerman *et al.*, 1972; Peach 1977). An improvement in renal function secondary to increased cardiac output, an increase in renal blood flow as the vasoconstrictor effects of angiotensin II dissipate, and the decreased stimulus for sodium and fluid retention as aldosterone concentrations fall, may help to promote a diuresis that further reduces preload.

The acute effects of captopril on resting haemodynamic measurements in our group of 15 patients were similar to those reported in previous studies. At peak drug effect, the systemic vascular pressure

decreased by a mean of 38%, cardiac and stroke indexes rose by 25% and 32% respectively, and there was a mean reduction of 42% in left ventricular filling pressure. These beneficial changes were important in documenting a response to therapy typical for patients with coronary heart failure, but they occurred when our patients were inactive and thus asymptomatic. In contrast to most previous studies, all our patients were ambulatory outpatients who were clinically stable, with symptoms predominantly during exertion. Because our patients were able to exercise, we sought to determine whether captopril exerted beneficial haemodynamic effects during symptomatic activity and whether there was an association between these drug effects and subsequent changes in exercise capacity.

Our results establish that captopril exerts a beneficial effect during upright exercise, with haemodynamic changes similar to those occurring at rest. Since the exercise haemodynamic measurements were made 90 minutes after drug administration rather than at peak effect, there was only a modest increase in cardiac index. Nevertheless, this cardiac index was achieved at a lower maximum heart rate and higher stroke index than the baseline performance, with both changes statistically significant. Importantly, the rise in left ventricular filling pressure with exercise was blunted and the systemic vascular resistance decreased an additional 13% during post-captopril exercise. This acute haemodynamic improvement was not, however, matched by an immediate improvement in exercise capacity. Exercise duration, maximum work load, and maximum oxygen consumption were unchanged on acute therapy.

This dichotomy disappeared in the six patients who continued to take long-term captopril treatment. At three months not only were the haemodynamic benefits of captopril at rest and during exercise sustained in these patients, but all three measurements of exercise capacity were now improved. At rest, captopril continued to cause a significant increase in cardiac index and reduction in left ventricular filling pressure.

While mean arterial pressure had returned toward its baseline levels, the systemic vascular resistance remained lower as a result of the sustained increase in cardiac index.

The haemodynamic benefit of long-term treatment was even more apparent during exercise. The cardiac index, which rose modestly and insignificantly after acute captopril administration, further increased by 18% on sustained treatment, and improved overall by 28% from the baseline. Similarly, the exercise stroke index rose an additional 17%, and the abnormal increase in left ventricular filling pressure showed further attenuation, rising to a mean of 26 mm Hg after three months of treatment.

But, most importantly, the sustained improvement in rest and exercise haemodynamic measurements was transformed clinically into an increase in exercise capacity. Each of the six patients was able to increase his exercise duration by a minimum of two minutes, exercising at least one work load stage higher and achieving a higher oxygen consumption.

In summary, we have shown that captopril produces beneficial haemodynamic changes at rest and during upright exercise in ambulatory patients with typical, chronic congestive heart failure. These changes, while important, are not associated with an immediate improvement in the functional capacity of the patient. In a small group of patients maintained on captopril for three months the acute haemodynamic benefit was not only sustained but appeared to increase further, especially during exercise. During long-term therapy the haemodynamic improvement was accompanied by an increase in exercise capacity. These results substantiate the effectiveness of maintenance captopril therapy in the treatment of chronic heart failure.

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