Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomised double blind placebo controlled trial

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Abstract

Objective—To determine the efficacy and dose requirements of captopril to reduce functional mitral regurgitation in patients with dilated heart failure.

Design—A randomised double blind placebo controlled parallel arm trial. Incremental daily doses of 25 mg, 50 mg and 100 mg captopril used for a four week period each for a total of 12 weeks preceded by a two week placebo washout. Twenty eight ambulatory patients (mean age 72) New York Heart Association (NYHA) class II or III with apparently controlled ischaemic dilated heart failure (ejection fraction 29% (0.04%)) on digoxin, diuretics, and nitrates were randomised. All had at least grade 2/4 functional mitral regurgitation (>5 cm² regurgitant area on colour flow Doppler).

Results—Twenty three patients completed the study (13 on placebo and 10 on captopril). Significant improvements were confined to the captopril group. Compared with placebo the following improvements were noted in the captopril treated group: mitral regurgitant area decreased from a threshold at 50 mg/day ($p < 0.05$, mean (95% confidence interval (95% CI)) 3.1 (0.2 to 6.0) cm²), with a further decrease at 100 mg/day ($p < 0.01$, mean (95% CI) 5.3 (3.1 to 7.5) cm²). Significant improvements in all the other measurements were noted only after 100 mg/day. Stroke volume increased ($p < 0.01$, mean (95% CI) 11, (1.4 to 21) ml), systemic vascular resistance decreased ($p < 0.05$, mean (95% CI) 414 (35 to 793) dyn s cm⁻²), left atrial area decreased ($p < 0.05$, mean (95% CI) 4.3 (0.03 to 8.6) cm²), and deceleration time increased ($p < 0.01$, mean (95% CI) 52 ms (7 to 98) ms). Left ventricular diameter decreased marginally ($p = 0.06$, mean (95% CI) 4 (-0.05 to 9) mm). Duke activity index score increased ($p < 0.001$, median (95% CI) 6.8 (4.5 to 12) points). Heart rate, mean arterial blood pressure, serum creatinine, and serum potassium did not change with either placebo or captopril. No patient was withdrawn directly due to the side effects of captopril. In an open phase nine placebo patients given captopril in rapid increments reaching 100 mg/day in the fourth week showed similar improvements.

Conclusion—Captopril is efficacious in reducing functional mitral regurgitation

in dilated heart failure. Patients require and must tolerate high doses (50–100 mg/day) for additive effects over supervised conventional treatment to occur.

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Functional mitral regurgitation is a consistent finding in dilated heart failure¹ leading to a vicious cycle of ventricular and atrial overload, increase in pulmonary wedge pressure,² and congestive symptoms. Load reduction with vasodilators redirects mitral regurgitation forward both at rest³ and after exercise⁴ thereby increasing cardiac output, improving ventricular and atrial geometry with a further decrease in mitral regurgitation. This results in sustained improvement in symptoms. Although the acute haemodynamic effects of the angiotensin converting enzyme (ACE) inhibitor captopril are known,⁵ its ability to reduce functional mitral regurgitation in dilated heart failure has not been investigated in a placebo controlled study. Moreover the optimal dose of captopril for dilated heart failure is unknown and there is a tendency among both British and North American prescribers to use subtherapeutic doses especially in elderly patients for fear of side effects.^{6,7} Recent evidence suggests that low dose compared with high dose ACE inhibitor treatment is associated with higher mortality.⁸ In our heart failure data bank of 233 cases enrolled over the past two years the overall prevalence of functional mitral regurgitation was 51%, with 37% having functional mitral regurgitant jets >5cm² on colour flow Doppler (regurgitant grade 2/4 or higher). Yet overall only 9.4% were on high dose ACE inhibitor treatment (>50 mg captopril/day or >10 mg enalapril/day); most were on lower doses. Residual mitral regurgitation may reflect ineffective or inadequate treatment.

By means of colour flow Doppler echocardiography we studied the efficacy and dose requirements of captopril in reducing functional mitral regurgitation. The trial was a randomised double blind placebo controlled parallel arm study on ambulatory patients with dilated heart failure and functional mitral regurgitation.

Patients and methods

Twenty eight ambulatory patients with chronic stable heart failure were enrolled. They had a mean (range) age of 71.6 (57–80)

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years and were New York Heart Association (NYHA) grade II or III, with dilated left ventricles (left ventricular end diastolic diameter on M mode >6 cm), ejection fraction <40%,⁹ and a functional mitral regurgitant area >5 cm² on colour flow Doppler. All except one were men. Twenty seven patients had had previous myocardial infarcts and the other had an idiopathic dilated cardiomyopathy. The heart failure was apparently controlled on digoxin, diuretics and nitrates. Four on low dose captopril (≤ 25 mg/day) and one on enalapril (5 mg/day) had their ACE inhibitors withdrawn. Exclusion criteria were myocardial infarction within the preceding three months, unstable or severe angina pectoris, valvar heart disease, serum creatinine >0.18 mmol/l, a history of alcohol misuse, and ACE inhibitor treatment of either >25 mg of captopril or >5 mg of enalapril a day. The protocol was approved by the hospital ethics committee and informed consent was obtained from each patient.

PROTOCOL

After a two week placebo washout period each patient was given a test dose of oral captopril (6.25 mg) and blood pressure was monitored for four hours. The patients without hypotension were randomised to active captopril or matching placebo, starting with 6.25 mg twice daily in the first week and after a satisfactory interview the dose was incrementally increased so that each received 12.5 mg twice daily at the end of four weeks, 25 mg twice daily at the end of eight weeks, and 50 mg twice daily at the end of 12 weeks. At each four weekly review, clinical assessment, blood tests for haematology and biochemistry, and cross sectional echocardiography with spectral and colour flow Doppler were performed. Conventional treatment was continued with adjustments to diuretics as required by weight changes. The patients were under constant supervision by a cardiac nurse through home visits and telephone contacts. After completion of the double blind phase, consenting patients on placebo were given open label captopril in incremental doses reaching 100 mg/day by the fourth week and were reassessed.

INSTRUMENTATION

An Acuson 128 cardiac colour flow Doppler system with a 2.25 MHz transducer for cross sectional imaging and a sample size of 5 mm for pulsed Doppler analysis was used. All measurements were made by the machine on line computer. Left ventricular end diastolic diameter was measured by cross sectional guided M mode.¹⁰ The left ventricular outflow stroke integral (LVSI (cm)) was measured by pulsed Doppler sampling in the left ventricular outflow tract from the apical long axis view. Stroke volume (ml) = $LVSI \times 3.14 \times (D/2)^2$, where D = left ventricular outflow diameter (cm) at the aortic annulus obtained from the long axis view.¹¹ This diameter was assumed to remain constant for the serial measurements. Mitral regurgitation

was assessed from the apical four chamber view by measuring the maximal area of the regurgitant jet on colour flow Doppler,¹² which included the aliasing and non-aliasing jet areas. Equipment settings that included the colour variance maps, frame rate, and depth were kept constant for each patient but gain was optimised to a level just below the point of appearance of noise artefact. Left atrial area was measured with planimetry from the frozen apical four chamber view at end systole. The left ventricular diastolic filling was assessed by sampling transmitral flow at the tip of the mitral valve from an apical four chamber view.¹³ Special emphasis was made on the deceleration time of the early filling (E) wave. A shortened deceleration time is known to be associated with raised filling pressures and high diastolic pressures.^{14 15}

DERIVED HAEMODYNAMICS

Arterial blood pressure (BP) was estimated by cuff sphygmomanometry (Dynamap):

$$MAP = \frac{SBP - DPB}{3} + DBP; CO = SV \times HR;$$

$$SVR = \frac{MAP - RAP}{CO} \times 80$$

MAP = mean arterial blood pressure (mm Hg); SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); CO = cardiac output (l/min), SV = stroke volume (ml); HR = heart rate (beats/min); SVR = systemic vascular resistance (dyn.s.cm⁻⁵); RAP = right atrial pressure, which was assumed to be 10 mm Hg for all studies.

The Duke activity status index¹⁶ has been shown to have a reasonable correlation with maximum oxygen consumption at peak exercise and is a good measure of functional capacity. It ranges from a minimum score of 2.75 points for activities of daily living (independence in dressing and bathing) to a cumulative total of 58.2 points for one who is playing strenuous sports. This was assessed at randomisation and at the end of the 12 week study.

WITHIN OBSERVER VARIABILITY

One investigator, who was blinded, assessed the clinical state and performed all the Doppler echocardiographic studies. Readings were averaged over three cycles for patients in sinus rhythm and over five cardiac cycles for the five patients in atrial fibrillation. The variability of left ventricular stroke volume was assessed at 3.1% (0–5 ml). Within observer variability for mitral regurgitant area was 6% (0–1 cm²). Day to day variation in mitral regurgitation in dilated cardiomyopathy is known to be about 15% (NS).¹⁷ Hence a >30% reduction in jet area would be needed to predict a therapeutic response at the level of the 95% confidence interval (95% CI). Twenty two patients completing the study would enable an adequate analysis at the level $p < 0.05$ with 80% power.

Table 1 Baseline characteristics (mean (SD)) of patients completing the trial

	Captopril (n = 10)	Placebo (n = 13)	p Value
Age (yr)	72.3 (5.4)	71.5 (7.2)	0.77 (NS)
Arterial pressure (mm Hg)	99 (13.8)	93 (9.8)	0.17 (NS)
Duke activity status index	21.5 (7.8)	22.6 (11)	0.91 (NS)
Left ventricular end diastolic diameter (cm ²)	6.4 (0.3)	6.4 (0.5)	0.47 (NS)
Mitral regurgitant area (cm ²)	8.1 (2.4)	9.0 (2.4)	0.25 (NS)
Stroke volume (ml)	43 (9.6)	42 (10.4)	0.49 (NS)
Systemic vascular resistance (dyn.s.cm ⁻⁵)	2274 (573)	2257 (576)	0.96 (NS)
Left atrial area (cm ²)	30.1 (5.5)	31.9 (6.7)	0.42 (NS)
Creatine (mmol/l)	0.13 (0.02)	0.13 (0.02)	0.93 (NS)

One patient taking captopril was a woman; three patients taking captopril and two taking placebo were in atrial fibrillation.

STATISTICS

Within group and between group comparisons were made by one and two way analysis of variance with paired and unpaired Student's *t* tests as appropriate. The 95% CIs were calculated. The results of the Duke activity status index were analysed with the Mann-Whitney U test.

Results

Twenty three patients completed the study (10 on captopril, 13 on placebo, table 1). Of the five withdrawals, four were in the captopril and one was in the placebo group. No patient withdrew due to a direct effect of captopril. Two patients were withdrawn by their physicians a few days after randomisation to captopril; one had a recurrence of a severe endogenous depressive illness, another developed an unrelated illness, but both continued to take captopril outside the trial. One on placebo died suddenly after an acute myocardial infarction.

Table 2 Response to captopril v placebo (mean (SD))

	Baseline	25 mg/day	50 mg/day	100 mg/day
Mitral regurgitant area (cm ²):				
Placebo	9 (2.4)	7.3 (3.3)	7.1 (3.4)	7.1 (2.9)
Captopril	8.1 (2.4)	6.2 (2.9)	4.0 (3.3)*	1.8 (2.0)**
Stroke volume (ml):				
Placebo	42 (10.4)	47 (11.9)	52 (14.7)	49 (8.9)
Captopril	43 (9.6)	50 (12.4)	51 (8.7)	60 (13.4)**
Systemic vascular resistance (dyn.s.cm ⁻⁵)				
Placebo	2257 (576)	2122 (656)	1928 (638)	1984 (473)
Captopril	2274 (573)	2036 (581)	1824 (449)	1570 (374)**
Left atrial area (cm ²):				
Placebo	31.9 (6.7)	30.8 (2.6)	30.9 (3.5)	31.4 (5.4)
Captopril	30.1 (5.5)	29.1 (5.0)	28.3 (4.1)	27.1 (4.1)*
Deceleration time (s):				
Placebo	175 (44)	189 (42)	174 (53)	191 (61)
Captopril	167 (43)	192 (48)	200 (31)	243 (38)**
Left ventricular end diastolic diameter (cm ²):				
Placebo	6.4 (0.5)	6.3 (0.5)	6.4 (0.6)	6.5 (0.6)
Captopril	6.4 (0.3)	6.2 (0.3)	6.2 (0.3)	6.1 (0.4)
Mean arterial pressure (mm Hg):				
Placebo	93 (9.8)	94 (12.4)	92 (12.8)	93 (10.8)
Captopril	99 (13.8)	96 (15.0)	93 (17.6)	94 (14.7)
Heart rate (beats/min):				
Placebo	77 (12)	76 (12)	74 (12)	72 (10)
Captopril	77 (16)	75 (15)	75 (11)	78 (10)
Plasma creatinine (mmol/l):				
Placebo	0.13 (0.02)	—	—	0.13 (0.03)
Captopril	0.13 (0.02)	—	—	0.13 (0.03)
Duke activity status index:				
Placebo	22.6 (11)	—	—	22.3 (9.8)
Captopril	21.5 (7.8)	—	—	29 (8.9)***

* p < 0.05; ** p < 0.01; *** p < 0.001.

Figure 1 Mitral regurgitant area (mean (SEM)) versus captopril dose.

MITRAL REGURGITANT AREA

Table 2 and figure 1 show that mitral regurgitant area did not decrease significantly in the placebo group (*F* = 1.26; *p* = 0.29) whereas a significant decrease, compared with both baseline and placebo, was found in the captopril group (*F* = 9.87; *p* < 0.001). Compared with placebo captopril decreased mitral regurgitation from a threshold dose of 50 mg/day (*p* < 0.05; mean (95% CI) 3.1 (0.2 to 6) cm²) with a further decrease at 100 mg/day (*p* < 0.01; mean (95% CI) 5.3 (3.1 to 7.5) cm²).

STROKE VOLUME AND SYSTEMIC VASCULAR RESISTANCE

Table 2 and figure 2 show that stroke volume did not increase significantly in the control group (*F* = 1.92; *p* = 0.01) but a significant increase was noted at a threshold of 100 mg of captopril daily (*F* = 3.64; *p* < 0.02).

Differences in favour of captopril compared with placebo were noted only after doses of 100 mg/day (*p* < 0.01; mean (95% CI) 11

Figure 2 Stroke volume (mean (SEM)) versus captopril dose.

Figure 3 Systemic vascular resistance (mean (SEM)) versus captopril dose.

(1.4 to 21)ml). Table 2 and figure 3 show that systemic vascular resistance did not decrease in the placebo group whereas a significant decrease in favour of captopril was noted at 100 mg/day ($p < 0.01$; mean (95% CI) 414 (35 to 793) dyn.s.cm⁻⁵).

LEFT ATRIAL AREA

Left atrial area did not decrease with placebo ($F = 0.13$; $p = 0.9$) but decreased with captopril after the 100 mg/day dose ($p < 0.05$; mean (95% CI) 4.3 (0.03 to 8.6) cm² (table 2, fig 4).

DECELERATION TIME

Table 2 and figure 5 show that the deceleration time of the E wave did not increase after placebo ($F = 0.39$; $p = 0.7$). Significant differences in favour of captopril were seen, marginally after 50 mg/day and maximally at the 100 mg daily dose ($p < 0.01$; mean (95% CI) 52 (7 to 98) ms).

LEFT VENTRICULAR END DIASTOLIC DIAMETER

Left ventricular diameter did not decrease with placebo ($F = 0.2$). Although there was a trend suggesting a decrease after 100 mg/day

Figure 4 Left atrial area (mean (SEM)) versus captopril dose.

Figure 5 Deceleration time (mean (SEM)) versus captopril dose.

of captopril this did not reach significance ($p = 0.06$; mean (95% CI) 4 (-0.05 to 9 mm) (table 2).

DUKE ACTIVITY INDEX SCORE

Table 2 and figure 6 show that the Duke activity index score increased by a (median 95% CI) of 6.8 (4.5 to 12) points after 100 mg/day of captopril whereas there was no improvement with placebo (Mann-Whitney U test; $p < 0.001$).

Heart rate, systolic blood pressure, mean arterial pressure, serum creatinine, and serum potassium concentrations did not change with either placebo or captopril. Three patients in the placebo group required an increase in diuretic dose to control weight gain. Of the five patients who had their low dose ACE inhibitors withdrawn, three were randomised to placebo and none deteriorated clinically or haemodynamically during the 12 week study.

OPEN PHASE

Nine patients on placebo agreed to take open label captopril given in rapid increments to reach 100 mg/day in four weeks. All nine completed this phase. Mitral regurgitation area decreased ($p < 0.002$; mean (95% CI) 4.6 (3.6 to 5.7) cm²). Stroke volume increased ($p < 0.002$; mean (95% CI) 12 (6 to 19) ml).

Figure 6 Duke activity index score (mean (SEM)) versus captopril dose.

Deceleration time increased ($p < 0.03$; mean (95% CI) 32 (4 to 61)ms). Systemic vascular resistance decreased ($p < 0.09$; mean (95% CI) 522 (175–870) dyn.s.cm⁻⁵). Duke activity increased ($p < 0.01$; mean (95% CI) 4.5 (0.9–8.1) points). The mean arterial pressure, heart rate, systolic blood pressure, left atrial area, and left ventricular end diastolic diameter did not change significantly. These findings are comparable with those obtained on 100 mg/day at the end of 12 weeks with the exception of the left atrial area.

Discussion

Our study shows that captopril is efficacious in reducing functional mitral regurgitation in patients with dilated heart failure (with NYHA class II or III symptoms), but a dose of at least 50–100 mg/day is required to show significant additive effects over supervised conventional treatment. These doses, reached by gradual increments, were safe and well tolerated even in an elderly population and there was no reduction in renal function or mean arterial blood pressure. As noted in previous studies the placebo group showed an improvement in some haemodynamics although this was not significant. This improvement may reflect the intense supervision of the cardiac nurse in ensuring drug compliance.

Captopril reduced mitral regurgitant area by 50% after 50 mg/day and by 77% after 100 mg/day whereas placebo caused only a maximum reduction of 21%, which was not significant. Reduction of mitral regurgitation would reduce left ventricular and left atrial loading with decreased left atrial size and decreased left ventricular filling and wedge pressures. A significant reduction in left atrial size was seen after the 100 mg daily dose. A smaller left atrial size resulting from the decrease in size of the atrioventricular orifice would decrease mitral regurgitation further and may prevent or delay the onset of atrial fibrillation. A decrease in left ventricular filling and end diastolic pressure was reflected by a significant lengthening of the deceleration time of the early filling Doppler (E) wave. This signals an easing of the restrictive physiology seen with high filling pressures.^{14 15} At least 100 mg/day was needed to show significant increases in stroke volume and reduction in systemic vascular resistance. The Duke activity status index score improved by an average of 6.9 points with captopril at the end of 12 weeks whereas there was no improvement with placebo ($p < 0.001$). This could be translated to an improvement in a patient who was once limited to light work in the house being able to do moderate work, such as carrying groceries and working in the garden.

Left ventricular diameter decreased with captopril but this did not reach significance ($p = 0.06$). Previous work has shown a reduction in left ventricular volume after reduction in mitral regurgitation with vasodilator treatment.³ Measurement by M mode would be

too insensitive to show changes in left ventricular volume. Recently the studies of left ventricular dysfunction (SOLVD) group showed by ventriculography that long-term enalapril treatment resulted in a sustained reduction in left ventricular volume whereas there were progressive increases in left ventricular volume in the placebo treated group.¹⁸ The mechanism of this effect was not clear. It is tempting to postulate that, among other effects, ACE inhibitor treatment may have reduced the functional mitral regurgitation common in NYHA class II and III heart failure.

The presence of functional mitral regurgitation in congestive heart failure is, we believe, a marker of clinical importance. It identifies a group of patients most likely to benefit from vasodilator treatment.¹⁹ In patients, as our study group, already on conventional treatment or taking low dose ACE inhibitors its presence indicates inadequacy of treatment for load reduction. Based on the premise that vasodilators redirect regurgitant flow to increase forward stroke volume, increasing the dose of vasodilators would lead to increased cardiac output without a drop in mean arterial pressure, as was found in our study. Patients with dilated heart failure do not necessarily require high filling pressures to maintain cardiac output; they could function well at normal filling pressures.²⁰ Hence aggressive treatment is both safe and warranted.

Although the acute haemodynamic effects of captopril are independent of dose (12.5–100 mg) they do not predict the long-term response.²¹ A sustained effect depends on a relatively high dose that is the cornerstone of chronic treatment.²² Exercise capacity improves gradually over four to six weeks after fixed doses of captopril. To make allowances for this time effect each dose period was four weeks in our study. Hence the haemodynamic changes at the end of four weeks would be a valid reflection of the effects of the respective doses. There was no improvement in any of the measurements at the fourth week (25 mg/day) and even after eight weeks (50 mg/day) improvements in mitral regurgitation and deceleration time were only just perceptible. Yet in the open phase trial significant improvements were noted in four weeks (100 mg/day) comparable with those seen at 12 weeks in the graded study. Of three patients who had their low dose ACE inhibitors withdrawn and who were randomised to placebo, none deteriorated clinically or haemodynamically after 12 weeks. Although this is not absolute proof, these data support the importance of dose overriding time, but it is still conceivable that the lower dose (50 mg/day) given over a longer period than eight weeks could lead to further improvement. Hence a larger trial is now planned to compare 50 mg/day with 100 mg/day captopril in a similar group of patients over 16 weeks. This will also reduce the inherent risk of type 2 error as in our current study where the numbers were smaller.

LIMITATIONS

Our findings on dose requirements of captopril would be applicable to patients with dilated heart failure and functional mitral regurgitation; the optimal dose requirements of patients with less left ventricular dysfunction may well be lower. The assessment of mitral regurgitation by colour flow Doppler is semi-quantitative and the regurgitant area reflects the free jet momentum (incorporating the driving force and the flow rate) and to a lesser extent left atrial compliance, assuming that machine factors are kept constant. All our patients had central free jets best seen in the apical view and the equipment settings were kept constant for serial studies. The driving force may have actually increased as the blood pressure remained unchanged and the left atrial pressure was presumed to have decreased. Hence a reduction in the regurgitant area would indicate a decrease in flow rate and volume. Recent work has shown that colour flow imaging of jet areas are valid for quantitative assessment of mitral regurgitation in ischaemic or functional regurgitation where the jets are almost always central.²³ The Doppler measurement of stroke volume has been previously validated¹¹; the errors in measurement of the left ventricular outflow diameter were minimised by assuming that the diameter remains constant in the serial studies. Although the combination of a shortened left ventricular isovolumetric relaxation time, shortened deceleration time of the E wave, and an increased E/A (early to atrial filling) ratio best predicts increased left ventricular filling pressures¹⁵ we chose to use only the deceleration time as we have found this to be the easiest and the most reproducible to record. A long deceleration time reflected a fall in filling pressures and is known to be independent of the degree of mitral regurgitation.¹⁵ The singular value of deceleration time in assessing left ventricular filling pressures in the presence of left ventricular dysfunction has been emphasised recently.²⁴

In conclusion captopril reduces functional mitral regurgitation in dilated heart failure when given in adequate doses (50–100 mg/day). Residual mitral regurgitation in patients with heart failure may be a marker of suboptimal treatment. Such patients may form a sizeable proportion in outpatient clinics and they need and tolerate large dose treatment even if they are elderly. We confirm that Doppler echocardiography is a valuable method to detect mitral regurgitation, which is often silent, and is useful to monitor the haemodynamic response and titrate treatment in patients with dilated heart failure.²⁵

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