Investigators and editors should be encouraged to recognise the seriousness of publication bias and to submit and accept, respectively, well-conducted studies directed at important questions, no matter what the outcome.

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Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition

NORMAN SHARPE HEATHER SMITH JUDY MURPHY
SALLY GREAVES HAMISH HART GREG GAMBLE

Left ventricular dysfunction can be improved with angiotensin-converting-enzyme inhibition started 1 week after myocardial infarction or later. To see whether earlier intervention may confer greater benefit, a double-blind study was carried out in which 100 patients with Q wave myocardial infarction, but without clinical heart failure, were randomly allocated treatment with captopril 50 mg twice daily or placebo starting 24–48 h after onset of symptoms. Left ventricular volumes were measured regularly during 3 months of treatment and after a 48 h withdrawal period by means of two-dimensional echocardiography. The placebo group showed significant increases in left ventricular end-diastolic (LVEDVI) and end-systolic (LVESVI) volume indices, with the ejection fraction unchanged. By contrast, the captopril group showed a slight but not significant rise in LVEDVI and a significant reduction in LVESVI with ejection fraction increased significantly. At 3 months there was a 4·6% difference in the change in ejection fraction from baseline between the groups ($p < 0.0001$). Most of the treatment benefit was evident at 1 month and there were no changes in left ventricular volumes after 48 h withdrawal of treatment at 3 months. Heart failure requiring treatment with frusemide developed in 7 patients in each group during the study period; 3 of these (1 captopril-treated, 2 placebo-treated) had to be withdrawn from the trial with severe heart failure requiring open treatment. Thus early treatment with captopril is effective in preventing the ventricular dilatation that can occur after Q wave myocardial infarction.

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Introduction

Existing treatment for clinical congestive heart failure is effective in producing sustained haemodynamic and symptomatic improvement and better ventricular function and survival,[1-3] but since many patients have severe

ADDRESS: **Department of Medicine, University of Auckland School of Medicine, Auckland Hospital, Park Road, Auckland, New Zealand** (N. Sharpe, FRACP, H. Smith, J Murphy, S Greaves, FRACP, H. Hart, FRACP, G. Gamble, MSc) Correspondence to Dr Norman Sharpe.

ventricular dysfunction at the time of clinical presentation, such treatment may be only palliative. Treatment of symptomless left ventricular dysfunction from a week after myocardial infarction or later seems to prevent further ventricular dilatation and may reduce the occurrence of heart failure.[4-6] Whether this treatment approach will result in long-term prognostic improvement for such patients remains unproven and is the subject of large-scale studies.

Because the potential for progressive ventricular dilatation exists from the time of myocardial infarction[7,8] and because of its prognostic importance,[9] intervention soon after myocardial infarction, rather than a week later, may provide greater benefit. The aim of our study was to determine the effects on ventricular size and function of angiotensin-converting-enzyme inhibition started 24–48 h after the onset of symptoms in patients with myocardial infarction.

Patients and methods

Patients with definite Q wave myocardial infarction who were clinically stable 24–48 h after the onset of symptoms were eligible for the study. Those with ongoing myocardial ischaemia, atrial fibrillation or other arrhythmias requiring treatment, valvular disease, clinical congestive heart failure, hypotension (systolic blood pressure below 90 mm Hg), chronic lung disease, renal impairment (serum creatinine above 0·20 mmol/l), or other serious concomitant diseases were excluded. Patients who had received thrombolysis after admission were considered for inclusion as long as evolution of Q waves was evident on electrocardiography. Eligible patients underwent two-dimensional echocardiography, and those with adequate image quality who gave informed consent and tolerated an open test dose of captopril 12·5 mg were included in the randomised study.

Patients were randomly allocated double-blind treatment with captopril or placebo. Separate randomisation was done for patients with anterior and inferior infarction. On the first day of treatment, captopril was given in a dose of 25 mg twice daily; it was increased to 50 mg twice daily on the second day and continued at this dose for 3 months. If substantial hypotension (systolic blood pressure below 80 mm Hg or causing symptoms) occurred, the dose was reduced and later increased according to blood pressure.

TABLE I—CLINICAL CHARACTERISTICS OF PATIENT GROUPS AT BASELINE

—	Captopril (n=50)	Placebo (n=50)
Mean (SD) age (yr)	59 (8) (range 40–74)	56 (9) (range 35–74)
Female/male	9/41	8/42
Mean (SD) weight (kg)	75 (13)	75 (13)
Infarct site		
Anterior	26	26
Inferior	24	24
No receiving thrombolytic treatment	38	34
Mean (SD) peak creatine kinase (u/l)	2368 (1265)	25 98 (1376)
No with previous myocardial infarction	7	6
No with previous hypertension	16	16
Mean (SD) blood pressure (mm Hg)		
Systolic	117 (19)	121 (16)
Diastolic	76 (12)	78 (11)

TABLE II—BASELINE ECHOCARDIOGRAPHIC MEASUREMENTS OF LEFT VENTRICULAR VOLUME

—	Mean (SD)		
	Captopril	Placebo	Normal* (n=50)
LVEDVI (ml/m²)	73·3 (16·5)†	68·4 (18·2)†	56·2 (9·0)
LVESVI (ml/m²)	44·2 (12·2)†	40·4 (13·1)†	25·7 (5·0)
SVI (ml/m²)	29·1 (7·4)	27·9 (7·5)	30·5 (5·3)
Ejection fraction (%)	40·2 (7·0)†	41·1 (6·4)†	54·4 (3·4)

*Normal values given in reference 4
†$p < 0.0001$ for comparison with normal values

TABLE III—REASONS FOR WITHDRAWALS DURING TREATMENT

—	Captopril	Placebo
Angina	4	2
Recurrent myocardial infarction	1	4
Ventricular septal defect	1	..
Hypotension	1	..
Heart failure	1	2
Non-compliant	1	1
Sudden death	3	2

Patients underwent clinical and echocardiographic assessment at 1 week, 1 month, and 3 months of treatment and finally after a 48 h treatment withdrawal period. Clinical congestive heart failure occurring during the trial period was treated with frusemide up to a dose of 80 mg daily, and patients who did not respond to diuretic treatment were withdrawn from the trial for open treatment. Patients with angina which did not respond to nitrates and beta blockers and which required coronary angiography were withdrawn, as were those with reinfarction. The study was approved by the Auckland Hospital ethics committee and informed consent was obtained from each patient.

The endpoints of the study were left ventricular volumes and function measured by two-dimensional echocardiography and the occurrence of clinical heart failure requiring diuretic treatment or withdrawal from the trial. A standard approach to echocardiographic examination was used as described previously.[4] The methods of analysis of the echocardiographic recordings together with the normal values for the method and within-observer variability have also been described.[4] Left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and stroke volume index (SVI) were derived by means of body surface area estimated at each assessment.

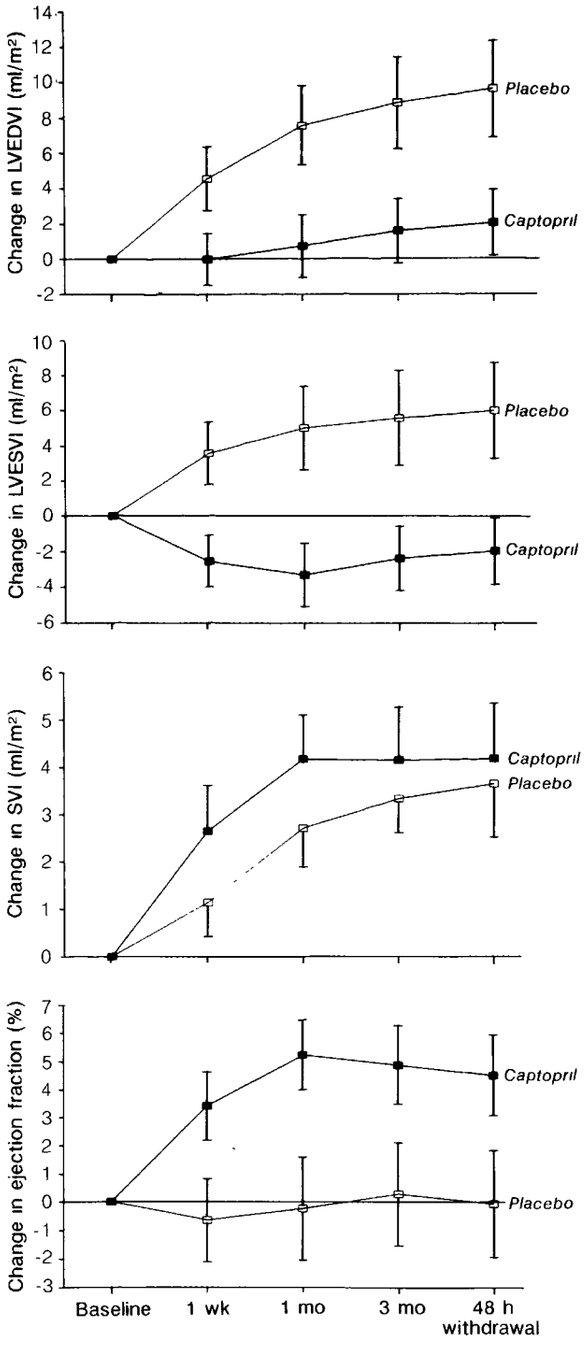
Site of myocardial infarction and the use of thrombolytic therapy were included in both multivariate analyses of variance[10-12] and a general linear model[12,13] to determine treatment effect size over repeated measures for each of the dependent variables. Results are presented as the F approximation to the Hotelling-Lawley trace.[11] Determinants of left ventricular volume change were sought from baseline variables by means of the Pearson product-moment correlation coefficient. A 5% significance level was adopted throughout.

Results

100 patients were selected for the study and randomly allocated treatment with captopril or placebo. Of 114 patients with Q wave myocardial infarction assessed for the study, 12 were excluded because symptomatic hypotension occurred after the test dose of captopril. The clinical characteristics of the placebo and captopril groups were similar (table I). There was a preponderance of male patients and a wide age range. The numbers of patients with anterior and inferior myocardial infarction were about equal, and 72% of all patients had received thrombolytic treatment.

Baseline echocardiographic measurements of left ventricular volumes and function were similar in the two groups (table II). LVEDVI and LVESVI were about 25% and 50% respectively, higher, than normal, whereas SVI was normal and ejection fraction was significantly lower than normal.

12 patients in the captopril group and 11 in the placebo group were withdrawn during the treatment period (table III). Additional drugs given during the treatment period were nitrates (5 captopril-treated patients, 6 placebo-treated), beta blockers (11, 10), calcium channel blockers (8, 11) frusemide (7, 7), digoxin (0, 4), and warfarin (3, 5).



Mean differences from baseline (95% CI) for left ventricular volumes and function.

The differences between the captopril and placebo groups in changes from baseline in left ventricular volumes were significant (LVEDVI $F_{(1,67)} = 20{\cdot}14$; LVESVI $F_{(1,67)} = 26{\cdot}70$; both $p < 0{\cdot}0001$). The mean differences from baseline are shown in table IV and the figure. The placebo group showed significant increases in LVEDVI and LVESVI from 1 week to 3 months; SVI also increased but ejection fraction did not change. By contrast, the captopril group showed no significant change in LVEDVI and a significant reduction in LVESVI from 1 week to 3 months, resulting in significant increases in SVI and ejection fraction. Most of the treatment benefit was evident within the first month, and at 3 months there was a 4·6% difference ($p < 0{\cdot}0001$) between the groups in the change in ejection fraction from baseline. There were no changes in left ventricular volumes after the 48 h treatment withdrawal period 3 months after baseline.

During the study period, 7 patients in each group were treated with frusemide. 3 of these patients (1 captopril-treated, 2 placebo-treated) were withdrawn from the study with severe heart failure requiring open treatment.

TABLE IV—DIFFERENCES FROM BASELINE IN LEFT VENTRICULAR VOLUMES

—	Mean (95% confidence interval)	
	Captopril	Placebo
Change in LVEDVI (ml/m²)		
1 wk	−0·03 (−1·53, 1·48)	4·56 (2·76, 6·36)
1 mo	0·71 (−1·27, 2·69)	7·59 (5·34, 9·84)
3 mo	1·57 (−0·61, 3·75)	8·83 (6·24, 11·42)
48 h withdrawal	2·04 (−0·16, 4·24)	9·59 (6·89, 12·31)
Change in LVESVI (ml/m²)		
1 wk	−2·54 (−4·01, −1·07)	3·57 (1·79, 5·35)
1 mo	−3·32 (−5·10, −1·54)	5·02 (2·65, 7·39)
3 mo	−2·38 (−4·20, −0·56)	5·58 (2·88, 8·28)
48 h withdrawal	−1·95 (−3·81, −0·09)	6·01 (3·31, 8·71)
Change in SVI (ml/m²)		
1 wk	2·65 (1·67, 3·63)	1·14 (0·14, 2·14)
1 mo	4·18 (3·36, 5·10)	2·72 (1·58, 3·86)
3 mo	4·16 (3·06, 5·26)	3·34 (2·34, 4·34)
48 h withdrawal	4·18 (3·00, 5·36)	3·65 (2·51, 4·79)
Change in ejection fraction (%)		
1 wk	3·41 (2·19, 4·63)	−0·64 (−2·11, 0·83)
1 mo	5·23 (4·00, 6·46)	−0·23 (−2·05, 1·59)
3 mo	4·87 (3·48, 6·26)	0·28 (−1·54, 2·10)
48 h withdrawal	4·51 (3·08, 5·94)	−0·05 (−1·93, 1·83)

5 patients (3 captopril-treated, 2 placebo-treated) were maintained on a trial medication dose of 25 mg twice daily throughout the trial because of low blood pressure. Blood pressure did not change significantly from baseline and was similar in both groups during treatment. There were no significant differences between the groups in serum urea, creatinine, or electrolytes during treatment.

Anterior and inferior infarct subgroups showed similar changes in left ventricular volumes and function. There was no significant correlation between baseline left ventricular volumes and subsequent changes in volumes, nor between peak creatine kinase at baseline and subsequent volume changes. There was no difference in treatment effect observed in the minority (28%) of patients who did not receive thrombolysis for any of the dependent variables.

Discussion

The rationale for treatment of symptomless left ventricular dysfunction is based on the known poor prognosis for heart failure and the fact that severe left ventricular dysfunction is present in many patients by the time congestive heart failure is manifest clinically. Progressive ventricular dilatation and dysfunction can occur after myocardial infarction and its extent is related to infarct size[14] and patency of the infarct-related artery.[15] Evolution of Q wave infarction may be followed by early infarct expansion[7] and later by progressive global ventricular dilatation.[8] Ventricular volumes are strong predictors of long-term survival,[9] and the frequency of congestive heart failure increases during the years after myocardial infarction.[16]

Clinical studies have shown that converting-enzyme inhibition can improve symptomless left ventricular dysfunction and possibly prevent congestive heart failure when treatment is started 1 week after myocardial infarction or later.[4-6] Also, partial reversal of progressive left ventricular dysfunction can be achieved with treatment after 1 year.[17] Our study shows the effectiveness of earlier preventive intervention.

The patient groups were well matched in terms of baseline clinical characteristics and ventricular volumes. The echocardiographic methods used depend on careful standardisation of recording and measurement techniques which have been established in our laboratory.[4] The values obtained are an underestimate of absolute left ventricular volumes[18] but provide a reliable measure of serial changes in a controlled study.

The optimum timing of this treatment after myocardial infarction is clinically important. In rats with myocardial infarction captopril has a beneficial effect on left ventricular performance, weight, and volume.[19,20] However, there was no difference in the benefit achieved at 4 months between oral treatment started 2 h after coronary ligation and treatment started at 21 days. This finding suggests that the primary effect of treatment may not be due to an effect on infarct expansion, which occurs in the majority of large infarcts by 7 days.[21,22] However, although immediate parenteral treatment might have been more effective than oral treatment, it is also possible that immediate treatment may confer some disadvantages which tend to reduce the overall benefit of treatment. Blockade of compensatory mechanisms activated at the time of infarction may not be desirable immediately after infarction, even though these mechanisms may be deleterious later. Although the rat model is useful for studies of left ventricular remodelling after myocardial infarction, patients with coronary artery disease may respond differently to converting-enzyme inhibition.

In contrast to the animal data, comparison of our study with previous clinical studies suggests that early treatment provides a greater benefit than later treatment. In our previous study,[4,6] we selected patients with Q wave infarction for treatment with captopril from 8–9 days after myocardial infarction for 1 year. Although captopril significantly reduced ventricular dilatation in contrast to the further dilatation that occurred with placebo, after 1 year of captopril treatment LVEDVI was still 30% and LVESVI still 50% higher than normal. Mean ejection fraction had improved from 37% to 44%. Thus, despite a beneficial effect from captopril treatment, most patients still had moderate left ventricular dilatation and dysfunction. In a further study,[17] a group of patients who had shown progressive ventricular dilatation during the first year after myocardial infarction were treated openly with captopril during the second year. Partial late reversal of left ventricular dilatation was achieved, but left ventricular function did not return to the baseline assessed 1 week after myocardial infarction.

Patients in this study had very similar baseline characteristics to those in our previous study,[4,6] although there were more patients with anterior infarcts in that study. In this study, ventricular dilatation, as expected, was less 24–48 h after myocardial infarction than at 1 week, but after 3 months ventricular volumes in the placebo groups from the two studies were similar. Earlier treatment not only prevented the substantial ventricular dilatation evident at entry to our previous study 1 week after infarction and at 1 week in the placebo group in this study, but it also improved ventricular function significantly from the earlier baseline. Thus, captopril treatment 24–48 h after infarction is feasible and provides a definite advantage over later treatment. Furthermore, selection of patients with Q wave infarction at 24 h, after thrombolysis, provides treatment for those most likely to benefit, which is well tolerated without significant risk of hypotension.

As in our previous study, we found no differential treatment effect in anterior or inferior infarct subgroups. We tested the hypothesis that treatment might be most beneficial in patients with large anterior infarcts (those with higher peak creatine kinase) who had not received thrombolysis and were thus less likely to have patent infarct-related arteries. No greater treatment benefit was evident in this subgroup. However, there were few patients in this analysis and a proportion of the other patients who had thrombolysis but still evolved Q waves would have had occluded infarct-related arteries.

The mechanism of improvement with captopril is not known, although the peripheral vasodilating effect is probably predominant and in this respect both preload and afterload reduction seem important.[23] Captopril may have a beneficial effect on the coronary circulation[24,25] and also direct effects on myocardial tissue[26,27] which are advantageous for long-term remodelling. The lack of significant left ventricular volume changes following a 48 h withdrawal at 3 months of treatment argues against an important short-term haemodynamic effect of captopril. Observation over a longer period would be required to determine whether there is any susceptibility to late dilatation after treatment withdrawal.

This study has shown that early treatment of patients after myocardial infarction with converting-enzyme inhibition provides an important ventricular function benefit during the first 3 months. Similar treatment in combination with or immediately after thrombolysis is being assessed in other studies but will necessarily be less selective. Further studies are required to assess the comparative and possibly additive effects of converting-enzyme inhibition, nitrates, and beta blockers in the postinfarction period. The results of larger studies are awaited to indicate the benefit of this type of treatment in terms of long term heart failure prevention and mortality benefit.

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Circulating Epstein-Barr virus-carrying B cells in acute malaria

K. M. C. LAM N. SYED H. WHITTLE D. H. CRAWFORD

Epstein-Barr virus (EBV) infection and *Plasmodium falciparum* malaria are two known cofactors in the aetiology of endemic Burkitt's lymphoma. To assess the relation between these factors, limiting dilution analysis was used to assess the number of EBV-carrying B cells in the circulation of Gambian children during and after acute malaria. Numbers of virus-carrying cells were five times higher in acute malaria patients and in UK patients with infectious mononucleosis than in convalescent malaria patients and in healthy control adults from the UK. Spontaneous outgrowth in limiting dilution cultures from acute malaria samples was inhibited by acyclovir, a viral DNA polymerase inhibitor. The mechanism of outgrowth, therefore, was virus release from the in-vivo infected cell, which led to infection and immortalisation of co-cultured normal B cells. The findings provide evidence that acute malaria is associated with an increase in the number of EBV-carrying B cells in the circulation. Because of this increase, there is a greater chance of a cytogenetic abnormality occurring in such a cell, with consequent evolution of Burkitt's lymphoma.

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Introduction

Endemic Burkitt's lymphoma (eBL) is a B-lymphocyte tumour with a high incidence in equatorial Africa and Papua New Guinea where it is the commonest childhood malignant disease.[1] Holoendemic *Plasmodium falciparum* malaria has an identical geographical distribution and is therefore thought to be a cofactor in the disease process. Two other factors, which are often associated with eBL, and are therefore implicated in the disease process, are Epstein-Barr virus (EBV) infection and a chromosomal translocation which deregulates the c-MYC oncogene.[2,3] These three steps in the evolution of Burkitt's lymphoma must act together on an individual cell to produce the tumorigenic phenotype.

To assess the importance of these stages in the aetiology of Burkitt's lymphoma, we have examined the association between persistent EBV infection and acute *P falciparum* malaria in children in The Gambia, West Africa, an area where malaria is holoendemic and where most children are already infected with EBV by 2 years of age.[4]

Subjects and methods

Subjects

Blood samples were obtained from eight subjects in each of five groups: Gambian children with acute malaria (group 1); the same Gambian children in convalescence 3 weeks after acute malaria (group 2); control Gambian children with mild infections unrelated to malaria (group 3); UK patients with infectious mononucleosis (IM) (group 4); and healthy UK adults (group 5). Samples from groups 1–3 were taken during the rainy season in The Gambia when acute attacks of malaria were frequent in young children. All patients with acute malaria had measurable parasitaemia which was undetectable in convalescent and control samples. All IM patients were Paul Bunnell positive at the time of sampling.

Limiting dilution analysis

To analyse the number of EBV-carrying B cells in the circulation we exploited the ability of EBV to immortalise B lymphocytes to yield lymphoblastoid cell lines.[5,6] Peripheral blood mononuclear cells (PMBC) were obtained by separation of whole blood over a

ADDRESSES: **Department of Clinical Sciences, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK** (K. M. C. Lam, PhD, N. Syed, BSc, Prof D. H. Crawford, MRCPath), **and MRC Laboratories, Fajara, Banjul, The Gambia** (H. Whittle, FRCP). Correspondence to Dr K. M. C. Lam.