Beneficial effect of enalapril on left ventricular remodelling in patients with a severe residual stenosis after acute anterior wall infarction


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Objective The present study was designed to evaluate the effects of early angiotensin converting enzyme (ACE) inhibition on left ventricular enlargement in patients with anterior wall infarction following reperfusion therapy.

Methods Seventy-one consecutive patients with an anterior wall myocardial infarction were randomly allocated to enalapril (n = 36) or placebo (n = 35). All patients received either thrombolytic therapy (n=46) or underwent primary coronary angioplasty (n = 25). Medication was started within 48 h admission to hospital and continued for 48 weeks. The process of left ventricular remodelling was assessed with two-dimensional echocardiography at 3 weeks and 1 year after the acute onset, and was related to the severity of the residual stenosis of the infarct-related artery.

Results Baseline left ventricular ejection fraction was 39.2 ± 8.7%. During the study period, left ventricular end-diastolic volume index increased from 48.2 ± 9.9 ml. m⁻² to 54.6 ± 12.2 ml. m⁻² at 3 weeks, and to 59.4 ± 17.0 ml. m⁻² after 1 year in control patients (P<0.001). In the enalapril-treated patients, left ventricular end-diastolic volume index increased from 47.0 ± 13.0 to 53.7 ± 17.7 ml. m⁻² compared to 48.0 ± 9.6 to 60.3 ± 16.3 ml. m⁻² in control patients (P<0.03). Also diastolic filling parameters were significantly improved in patients with >70% residual stenosis.

Conclusion In patients with an anterior wall infarction and a severe residual infarct-related coronary artery stenosis following reperfusion, treatment with enalapril prevents the process of left ventricular remodelling. As left ventricular dilatation is an early process we suggest that treatment with ACE inhibition should be started as soon as possible in this group of patients.

Key Words: Myocardial infarction, remodelling, coronary angioplasty, thrombolysis, enalapril.

Introduction

Loss of muscle fibres due to myocardial infarction imposes an excessive load on surviving heart muscle. The heart adapts to chronic load by a combination of dilatation and hypertrophy, called remodelling. Remodelling mitigates the effects of left ventricular dysfunction caused by infarction and improves pump function, but inflicts progressive damage on the heart and may shorten life expectancy.1

Thrombolytic therapy or primary percutaneous coronary angioplasty have been known to limit infarct size and to preserve viability of the remaining muscle, thus preventing subsequent cardiac events.2,3 Restoration of coronary blood flow is, however, not the only factor that is important. Treatment with angiotensin converting enzyme (ACE) inhibitors improves survival by preventing left ventricular hypertrophy and dilatation.4,5 In patients in whom left ventricular ejection...
fraction is below 40%, ACE inhibition improves survival significantly, irrespective of whether therapy is initiated soon after the infarction or many months later.[6-9] It was soon conjectured that ACE inhibitor therapy, if initiated very early after an infarction, could have beneficial effects other than reversal or prevention of remodelling.[10-12] Experimental data have shown that ACE inhibition in the acute stage of an infarction may limit infarct size by preventing infarct extension[10], possibly due to bradykinin-mediated vasodilation[11,12]. Moreover, complications of an acute infarction such as infarct expansion, aneurysm formation and ventricular rupture, all of which have a distinctly negative effect on survival, may be prevented because ACE inhibitors reduce the systolic wall stress that puts strain on scar tissue.[13-16] If ACE inhibitors have such additional beneficial actions, treatment should be indicated not only in patients with large infarctions and ejection fractions below 40%, but in all patients without any delay. A number of trials were designed and carried out, all aimed at demonstrating early beneficial effects of ACE inhibitor treatment on ventricular enlargement and/or survival.[17-27] These studies showed that only a limited number of infarct patients benefited from early ACE inhibitor treatment. Patients with transmural anterior wall infarctions were among the ones most likely to benefit.

The present study was designed to evaluate the effects of early ACE inhibition on left ventricular enlargement in patients with a documented anterior wall infarction treated with thrombolysis or coronary angioplasty in a randomized, double-blind fashion, using enalapril or placebo added to the standard medical regimen. In addition, we prospectively separated our patients into those with a <70% and those with ≥70% stenosis of the infarct-related artery. This was based on the hypothesis that a residual lesion of ≥70% after reperfusion may identify a subgroup for differential cardiovascular risk.[28-31] An ancillary aim of the study was to separate early (3 weeks) and late (one year) effects of ACE inhibition.

**Patients and methods**

Patients with electrocardiographic ST-segment elevation due to an acute anteroseptal or anterior wall infarction with peak creatine kinase plasma levels of at least four times the upper limit of normal were included in the study. Patients were admitted to the coronary care units of either the Leiden University Hospital or the Bronovo Hospital at the Hague, Netherlands. Patients with a history of clinically important renal, hepatic or haematological disorders, haemodynamically significant valvular disease, hypotension (systolic blood pressure <100 mmHg), or right-sided heart failure due to pulmonary disease were excluded. Patients in whom the echocardiogram was of insufficient quality were also excluded. The protocol was approved by the Ethical Committees of both hospitals. All patients gave written informed consent.

**Thrombolytic treatment and coronary angioplasty**

All patients received intravenously (1·5 x 10^6 units streptokinase) administered thrombolytic therapy (n=46) or primary angioplasty (n=25) within 6 h of the acute onset. The first dose of trial medication of 2·5 mg enalapril or placebo was given between 24 to 48 h after admission. The dosage was increased the next day to 2·5 mg twice a day only if systolic blood pressure was 100 mmHg or more. If systolic blood pressure fell below 100 mmHg or diastolic blood pressure below 65 mmHg, the dose remained at the same level, even if patients were completely asymptomatic. If blood pressure allowed such, the dose after 48 h of treatment was increased to 5 mg twice a day, followed by 10 mg once a day after 72 h, and to 20 mg once a day after 96 h. The dose was maintained at that level until 48 weeks after inclusion. Investigators and patients were blinded to the study medication.

**Blood pressure monitoring and blood sampling**

Within 24 h of admission, baseline data were collected. Mean blood pressure was calculated (Accutor, Datascop, Montvale, NJ, U.S.A.) from 10 measurements within 30 min. Directly following the blood pressure measurements, two-dimensional echocardiography was performed. During the first 3 days, blood samples were taken every 6 h for determination of serum α-hydroxybutyrate dehydrogenase (α-HBDH) levels to estimate infarct size.[21] Blood pressure measurements were repeated every day during the first 5 days. Three weeks after the acute event, patients returned to the outpatient clinic for blood pressure measurements and echocardiography. Echocardiography and blood pressure measurements were repeated 6, 9, 12, 24, and 48 weeks after admission. Patients were then asked to discontinue study medication and they returned 2 weeks later for a final echocardiographic study.

**Coronary angiography**

Coronary arteriograms were available in all patients. The patients who had undergone primary PTCA had repeat angiography within 4 days of the acute event; the patients who received thrombolytic therapy were catheterized at discharge (mean 7 days after the acute event). The coronary angiograms were quantitatively analysed with an automated contour detection technique (Cardiovascular Measurement System, MEDIS, Medical Imaging Systems, Nuenen, Netherlands) developed by Reiber et al.[32].
A luminal diameter stenosis of \( \geq 50\% \) was considered haemodynamically significant. All 71 patients had significant coronary artery disease. When stratified to a >70% residual stenosis, 43 (61%) patients (22 enalapril, 21 placebo) showed a haemodynamically significant stenosis of \( \geq 70\% \), and 28 (39%) patients (14 enalapril, 14 placebo) had <70% stenosis of the infarct-related artery. In all patients the infarct-related artery was invariably the left anterior descending coronary artery, showing TIMI flow of at least grade 3.

**Echocardiography**

Echocardiograms were made according to the guidelines proposed by the American Society of Echocardiography. All echocardiographic studies were performed by the same physicians in both centres who were blinded to treatment allocation. In one centre (Leiden University Hospital), a Vingmed CFM-750 echocardiographic machine was used (Sonotron, Trondheim, Norway), which was linked to a MacIntosh computer with Vingmed software for transfer, storage and analysis of digital ultrasound data. In the other centre (Bronovo Hospital, The Hague), the echocardiographic studies were carried out on a Toshiba SSH-65A (Toshiba Corp., Tokyo, Japan). The echocardiographic images were stored on tape and analysed off-line using the Vingmed equipment at Leiden University Hospital.

Patients were examined in the left lateral position, and recordings were made in complete expiration. Examination included a two-dimensional echocardiogram in the apical four chamber view and pulsed Doppler recordings of mitral flow and left ventricular outflow velocities. Concurrently, an electrocardiogram and a phonocardiogram were recorded to facilitate selection of end-systolic and end-diastolic frames. During each examination, series of end-systolic and end-diastolic images, usually pertaining to six cardiac cycles, were stored. All images were traced by a single observer. From the tracings, end-systolic and end-diastolic volumes were calculated using a disc summation method. Volume data calculated from six stored images were averaged. For these six images, the coefficient of variation, i.e. standard deviation expressed as percentage of mean, was only 3.5% for end-diastolic and 4.5% for end-systolic volumes33.

To assess diastolic function, echocardiographic Doppler spectra of pulsed wave flow-velocity curves of the mitral valve flow were traced. From these tracings the velocity–time integrals of early (Ei) and late (Ai) diastolic filling and total mitral flow (Tvi) were calculated. Diastolic properties of the left ventricle were evaluated by calculating Ei/Ai and AiTvi ratios.

**Statistical analysis**

To assess differences in left ventricular volumes or functional changes between both patient groups, two-way analysis of variance (ANOVA) was used. The two-factor analysis allowed evaluation of the independent and interactive effect of the actual volume and the use of treatment drug. Differences between treatment groups were analysed with paired and unpaired t-tests. In all statistical analyses, a \( P \) value <0.05 was considered statistically significant. Results are reported as mean value \( \pm \) 1 standard deviation (SD) between brackets.

**Results**

Baseline characteristics of the 71 patients are shown in Table 1. There were no significant differences in symptomatic status, reperfusion strategies, infarct size, and medical regimen between the enalapril and the placebo groups. Forty-two percent of patients fulfilled the criteria for symptomatic heart failure, as used in previous trials6.9. The mean left ventricular ejection fraction on admission was 37.7 ± 7.7% and 40.7 ± 9.4% in the placebo and enalapril groups, respectively (ns). There were no differences in extent and severity of coronary artery disease between either group. As almost all patients showed a systolic blood pressure of 100 mmHg or more, the 20 mg once daily target dose of study medication was reached in most of our patients, with a mean dose of 18.4 ± 4.3 mg in the placebo group and 18.6 ± 3.9 mg in the enalapril group. There were no notable adverse effects as a result of using the enalapril.

**Patient follow-up**

In the course of the study, 12 (17%) patients were withdrawn from randomization at 3 weeks; seven (10%) taking placebo, five (7%) taking enalapril. The reasons for withdrawal were hypotension (1 placebo, 2 enalapril), coronary angioplasty at discharge (2 placebo, 14
Haemodynamic effects

On admission, mean blood pressure was 89.8 ± 10.5 mmHg in the placebo group and 89.1 ± 11.3 mmHg in the enalapril group (ns). On the first day of the study, mean blood pressure was 86.1 ± 12.1 mmHg in the placebo group and 85.0 ± 12.8 mmHg in the enalapril group (ns). After the first dose of enalapril, mean blood pressure fell to 79.5 ± 10.2 mmHg in the treated group vs 85.2 ± 12.6 mmHg in the placebo group, and remained at a significantly lower level during the full study period in the treated group (P<0.002) (Fig. 1).

Left ventricular function

Both at 3 weeks and after 1 year left ventricular ejection fraction did not change significantly in either group during the study period (Table 2). In both treatment groups, the left ventricular end-diastolic volume index increased substantially during the study period (P<0.001) (Fig. 2). In most instances, this increase was achieved in the first 3 weeks following the acute event. Neither in the first period, which was mainly determined by regional infarct expansion, nor in the subsequent period was there any significant difference in the left ventricular end-diastolic volume index between the placebo and enalapril groups.

Diastolic function

The initial Ei/Ai ratios, derived from mitral flow patterns, were 1.21 ± 0.54 in the placebo-treated group, and 1.35 ± 0.60 in the enalapril-treated group. Over the 1 year follow-up period, the Ei/Ai ratios improved significantly to 1.42 ± 0.63 and 1.45 ± 0.73, respectively (both P<0.01). The atrial contribution to filling, estimated from the Ai/Tvi ratio, decreased from 0.48 ± 0.11 to 0.44 ± 0.10 in placebo-treated patients, and from 0.45 ± 0.10 to 0.44 ± 0.11 in enalapril-treated patients (both ns). Changes were not significantly different between the placebo and the enalapril-treated group.

Relation with residual stenosis severity ≥70% of the infarct-related artery

Table 3 is a contingency table showing left ventricular enlargement after 1 year in the remaining 56 patients and in the 36 patients with a residual stenosis of ≥70% of the infarct-related artery. For patients treated with enalapril who had a residual stenosis of ≥70%, the left
Table 2. Left ventricular end-systolic volume index (LVESVI), end-diastolic volume index (LVEDVI), and ejection fraction (LVEF) determined on admission, at 3 weeks, and after 1 year following acute myocardial infarction. Mean values and standard deviations are given for the placebo and the enalapril group. Differences between volume values at entry and those obtained one year later were all highly significant (P<0.001).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Enalapril</th>
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<tbody>
<tr>
<td>LVEDVI (ml·m⁻²)</td>
<td>48.2 ± 9.9</td>
<td>50.0 ± 16.1</td>
</tr>
<tr>
<td>LVESVI (ml·m⁻²)</td>
<td>30.4 ± 8.7</td>
<td>29.7 ± 11.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37.7 ± 7.7</td>
<td>40.7 ± 9.4</td>
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Figure 2. Ventricular enlargement (±1 SD) from admission to 1 year later in the final group of 56 patients. Overall, there is a significant increase in left ventricular end-diastolic index (P<0.001), but no significant differences between placebo and active treatment can be observed. *=controls; •=enalapril; <->=ns.

Discussion
In the present work left ventricular remodelling was studied in patients with anterior wall infarction who were treated in a randomized, double-blind fashion.
Table 3 Contingency table for placebo and enalapril-treated groups for the overall population and the subgroup with a residual infarct-related coronary stenosis ≥70%.

One year after myocardial infarction, complete data on ventricular enlargement as well as on cumulative α-HBDH release were available from 56 of the initial 71 patients, and from 36 of the initial 43 patients with a residual stenosis ≥70%. Ventricular enlargement is indicated by the difference between the left ventricular end-diastolic volume index (LVEDVI) after 1 year and before starting treatment. Patient groups with coronary stenosis ≥70% showed larger infarct sizes (*P<0.05) and a significant difference in ventricular enlargement between enalapril and placebo over time (*P<0.03)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>≥70%</th>
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<tbody>
<tr>
<td><strong>Total no. of patients</strong></td>
<td>n=56</td>
<td>n=36</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>n=27</td>
<td>n=17</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>163±10.9</td>
<td>18.8±10.3</td>
</tr>
<tr>
<td>α-HBDH (U.L⁻¹)</td>
<td>1022±587</td>
<td>1472±714*</td>
</tr>
<tr>
<td><strong>Enalapril</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>n=29</td>
<td>n=19</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>163±14.2</td>
<td>4.2±9.2**</td>
</tr>
<tr>
<td>α-HBDH (U.L⁻¹)</td>
<td>1366±990</td>
<td>1157±733</td>
</tr>
</tbody>
</table>

with enalapril or placebo. All patients had been treated with reperfusion therapy i.e. thrombolysis or primary coronary angioplasty. The main results of our study were threefold. First, the left ventricular end-diastolic volume index increased substantially during the study period in both treatment groups, and in most patients the increase was achieved in the first 3 weeks following the acute event. Second, no significant differences in left ventricular volumes between the enalapril and the placebo groups could be observed in the overall population either at 3 weeks or after 1 year. Third, when residual stenosis severity was ≥70% in the infarct-related artery, enalapril showed significant attenuation of left ventricular enlargement when compared to placebo. In this subgroup of patients diastolic functional parameters also benefited from enalapril.

Rationale for early ACE inhibition after myocardial infarction

Left ventricular enlargement has been shown to start very early after the onset of myocardial infarction. In this early phase, stretching of the infarcted zone due to slippage of the necrotic myofibrils occurs. Experimental studies have shown that angiotensin converting enzyme inhibition may improve survival of the ischaemic myocyte. To achieve optimal benefit it appears critical that the drug is able to reach the myocyte at risk. In the clinical setting this situation may best be created if treatment is initiated within the reperfusion time window. The early phase of left ventricular dilatation is a regional phenomenon of the infarct-related zone. This is followed by a second phase of dilatation, which involves the entire ventricle, and may continue for months after the acute event. The latter process consists, besides dilatation, of hypertrophy of the non-infarct-related

![Figure 3](image-url)
zone in response to the loss of contractile elements and increased wall stress. The complete process of dilatation and hypertrophy has been referred to as remodelling.\cite{Mac56}
To evaluate and compare treatment effects during the two processes the present study used serial echocardiography with major evaluation in the early phase (3 weeks) and in the late phase (one year). We selected patients with a transmural anterior wall infarction as they are particularly at risk for infarct expansion and therefore more likely to benefit from early ACE inhibition.\cite{Mac56}

**Previous studies**

Previous studies have shown that ACE inhibition improves survival in patients with left ventricular dysfunction\cite{Mac57-59}, and this effect is most likely due to attenuation of left ventricular remodelling.\cite{Mac57, Mac57'} Treatment with ACE inhibition within a week of infarction limits further dilatation of the left ventricle and has a beneficial effect on subsequent progression of heart failure.\cite{Mac538, Mac391}. In the PRACTICAL study, immediate administration of captopril and enalapril within 24 h of acute onset prevented left ventricular dilatation; the benefit was similar with both ACE inhibitors and was in excess of the benefits of optimal conventional therapy.\cite{Mac381}. The outcomes of the Fourth International Study of Infarct Survival (ISIS-4) and the Third Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-3) study indicated a modest but favourable effect on mortality when ACE inhibition was started within the first 24 h of myocardial infarction.\cite{Mac19-21} This beneficial effect of ACE inhibition was observed in addition to treatment regimens such as beta-blocking agents, anticoagulation, aspirin, and thrombolysis. Recently, investigators of the Captopril and Thrombolysis Study (CATS) reported that left ventricular enlargement is an early phenomenon that can be attenuated by early administration of captopril following thrombolytic therapy.\cite{Mac391}. The authors showed that captopril prevented progression to left ventricular dilatation in patients with intermediate-sized infarct size. In concordance with the CATS study our findings indicate that ventricular dilatation is mainly an early process and that potential effects of treatment may become apparent at this stage. In particular, our study revealed that patients with a residual stenosis of $\geq 70\%$ in the infarct-related artery are likely to benefit from early treatment with enalapril.

Thrombolysis and coronary angioplasty, although effective in limiting infarct size by restoring perfusion, will not resolve the culprit stenosis completely and often leave a haemodynamically significant stenosis.\cite{Mac409}. In the present study, 43 (61\%) of 71 patients were found to have a residual stenosis $\geq 70\%$ by digital quantitative analysis. The results of the present study demonstrate that in patients with such a stenosis, early treatment with enalapril effectively limits progression of left ventricular dilatation.

**Considerations of the study**

Several issues of the present study should be further considered. First, of the 71 patients who entered the study, 56 (79\%) patients had complete data after 1 year. This loss of data could have influenced our final results although the percentage of drop-outs was similar among both groups. Second, our sample size may have been too small to demonstrate any treatment effect at all in the overall population. We therefore additionally prespecified a particular subgroup of patients with a residual infarct-related stenosis of $\geq 70\%$. This stratification was based on the assumption that a 70\% stenosis or more bears a more adverse outcome than patients with $<70\%$ stenotic lesions.\cite{Mac28-31} In addition, the early phase of left ventricular dilatation is predominantly related to the infarct-related zone and any treatment effect may primarily be due to functional improvement of the infarct area.\cite{Mac29, Mac30}. Third, patients underwent two different reperfusion strategies, i.e. thrombolysis or primary angioplasty. These distinct strategies may have exerted different effects on left ventricular function. This may hold in particular for the thrombolysis group, as an open vessel at 7 days may not be proof of early recanalization because of spontaneous late recanalization. However, both interventions were similarly distributed among the enalapril-treated and the placebo group. Lastly, our study was not designed to assess the effects of acute ACE inhibitor therapy on mortality or morbidity. However, mortality and morbidity were carefully monitored because of concerns regarding the potential adverse effects of early ACE inhibition. In summary, our study shows that in patients with severe arteriographic stenosis and larger infarct sizes following reperfusion, early ACE inhibition has no detrimental effects and may even be beneficial in the long run.

**Conclusion**

In patients with an anterior wall infarction and a severe residual infarct-related stenosis following reperfusion, treatment with enalapril prevents the process of left ventricular remodelling. As left ventricular dilatation is an early process we suggest that treatment with ACE inhibition should be started as soon as possible in this group of patients.

**References**


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