Early vasodilator treatment in myocardial infarction: appropriate for the majority or minority?

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Abstract
Objective—To assess the influence of vasodilator treatment started early after myocardial infarction on left ventricular size and function.

Setting—Coronary care unit, Royal Infirmary, Edinburgh.

Patients—105 patients with acute myocardial infarction (systolic blood pressure > 90 mm Hg) were randomised within 24 hours of the start of pain. Unlike previous studies 88% of the patients received thrombolysis.

Methods—Double blind randomised placebo controlled study with either 12.5 mg of captopril three times daily or 20 mg of isosorbide mononitrate three times daily for 28 days.

Main outcome measures—Clinical outcome and left ventricular size and function assessed by echocardiography, radionuclide ventriculography, and magnetic resonance imaging.

Results—There was no difference in left ventricular size or function in either treatment group as measured one week after the end of the trial. Even the placebo group tended to decrease left ventricular diameter over the four week study period (one week: 5.0 (0-1) cm, five weeks: 4.8 (0-1) cm, NS). Four patients had an adverse clinical outcome in the placebo group whereas no adverse outcome was seen in the captopril group.

Conclusions—Vasodilator treatment may be of limited value or of no benefit for most infarct patients, particularly those treated with thrombolytic agents. Captopril, however, may benefit patients at high risk.

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In selected patients vasodilator treatment has been shown to prevent ventricular dilatation after infarction. It is not known if this is true for all patients, particularly those treated with thrombolyis.

Thrombolytic treatment has beneficial effects on both the mortality and residual left ventricular function after myocardial infarction. Moreover thrombolyis reduces infarct size and the proportion of patients with persistent occlusion of the infarct related artery—the two factors recognised as the most important determinants of ventricular dilatation. It seems likely that thrombolyis will modify the process of dilatation after infarction and therefore possibly the role of vasodilator treatment.

The aim of our study was to evaluate early vasodilator treatment in an unselected group of patients with acute myocardial infarction and therefore assess its role in the typical infarct patient.

As it is not clear which vasodilator might be most effective after acute myocardial infarcion, two drugs were investigated in this double blind randomised study. The first was the angiotensin converting enzyme inhibitor, captopril, which has been shown to be beneficial in selected infarct patients and also may reduce infarct size. The second drug was isosorbide mononitrate, one of the nitrate vasodilators, which as a group have been reported to reduce mortality and ameliorate left ventricular dysfunction after infarction.

Patients and methods
STUDY PROTOCOL
Patients admitted to the coronary care unit with suspected acute myocardial infarction were eligible for study, if they presented within 24 hours of the start of chest pain and the systolic blood pressure was > 90 mm Hg. Previous myocardial infarction was noted. The study was approved by the local ethics committee and informed consent was obtained from all participating patients.

TRIAL TREATMENT
Patients (n = 105) were randomised to one of three treatments: placebo (n = 36), 20 mg isosorbide mononitrate (n = 33), or 12.5 mg captopril three times daily (n = 36). Captopril was initially given at a test dose of 6.25 mg and if this was well tolerated the full dose was given two hours later. If patients became hypotensive the protocol permitted omission of a dose or the use of half dose. Blood pressure was monitored every 15 minutes for the first two hours after the test dose. If the trial drug was tolerated, patients underwent treatment for 28 days. Patients who were withdrawn and stopped treatment before completing one week of the trial did not participate further in the study and therefore were not assessed for left ventricular size and function.

IMAGING
Left ventricular imaging was performed by three different techniques, so as to benefit from
the strengths of each. Anatomical information was gained from echocardiography and nuclear magnetic imaging whereas cardiac function was assessed by radionuclide ventriculography. The main assessment of left ventricular size and function was performed at five weeks, one week after stopping drug treatment, as it is known that the pharmacological actions of vasodilators can influence these measurements. This protocol contrasts with the original work performed on captopril.\textsuperscript{12}

**Echocardiography**

Echocardiography was attempted in all patients at one and at five weeks after entry to the trial. Images were recorded on Hewlett-Packard echocardiography machines (both sonos 100 and 1000) with the patient lying semisupine in the semilieft lateral position. Where the patient would comply the recordings were made at the end of expiration. Images were measured on the short parasternal axis at the level of the mitral valve tips. The anteroposterior and transverse diameters of the left ventricular cavity were measured at this level by the Hewlett-Packard calculation package. The results are given as the mean diameter.

**Radionuclide Ventriculography**

Left ventricular ejection fraction was assessed by this radionuclide technique, five weeks after entry to the study. Patients were supine under a gamma camera (Siemens LEM) that was positioned in the modified left anterior oblique position with caudal tilt to provide good ventricular separation. The camera was interfaced to a Siemens' microdelta computer. The blood pool labelling was by injection of 700 MBq technetium-99m labelled human serum albumin (TCK2, CIS (UK) Ltd). After equilibration, an electrocardiogram gated acquisition of five million counts were made. The ejection fraction was calculated by a semi-automatic technique.\textsuperscript{13}

**Magnetic Resonance Imaging**

Patients were scanned roughly six weeks after the start of chest pain with a low field system (M and D Technology) operating at 0.08 tesla. A cardiac gating technique was used to synchronise acquisition of data during end diastole. Six or seven slices of 12 mm thickness and separation were required to obtain short axis views of the ventricular chambers from the cardiac apex to the outflow tracts. Two slices with a 32 ms time separation were obtained with each acquisition, which consisted of two averages of 128 frequency encoding steps and 64 phase encoding steps resulting in a pixel size of $3 \times 3$ mm. This data was interpolated to a $128 \times 128$ matrix ($3 \times 3$ mm) and smoothed on the final display monitor for image analysis. A double spin echo pulse sequence was used with echo delay times of 42 and 120 ms for the first and second echoes respectively. The repetition time was determined by the patient's heart rate but if this exceeded 95 beats/min data were only acquired every other heart beat.

The first echo image routinely provided good anatomical detail with clear delineation of the endocardial border. To obtain the left ventricular volume an irregular region of interest was drawn around the endocardial surface on all slices by image analysis software. The value obtained were then summed and multiplied by the slice thickness to produce the total left ventricular volume.

**Statistics**

Comparison between groups was performed by Mann-Whitney U test for continuous variables and $\chi^2$ test for the clinical outcome (Minitab release 6.1, Minitab, PA 16801, USA).

**Results**

**Baseline Characteristics**

The three groups were similar with respect to age, sex, site of infarct, and peak creatine kinase (table 1). The distribution of patients with previous myocardial infarcts was not even so these patients were not included in the assessment of clinical outcome and left ventricular size and function. One of the most striking characteristics of this study was that 88% of patients received thrombolysis with a mean time to thrombolysis of 3-2 hours. Most patients completed trial treatment.

**Reasons for Not Completing Trial Treatment**

Eighteen patients did not complete the trial (table 2). Five patients withdrew consent for trial participation shortly after entry into the study. One patient in the placebo group withdrew himself after 10 days because of breathlessness, later diagnosed as pulmonary oedema. A few patients were withdrawn for minor symptoms for example headache or indigestion. One patient developed glomerulonephritis which was attributed to streptokinase but despite this he was withdrawn from the trial.

The more serious reasons for withdrawal included reinfarction (one patient on captopril) and prolonged hypotension with impaired tissue perfusion (three patients all on placebo). Four patients died within the first 28 days. In the placebo group one died shortly after randomisation and the other died from cardiac rupture at four days. Both patients that died in the isosorbide group had cardiogenic shock (one with a history of myocardial infarction).

**Echocardiography**

Images were recorded from 89 out of the 105 patients. Image quality precluded quantitative

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Table 1  **Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 36)</th>
<th>Isosorbide mononitrate (n = 33)</th>
<th>Captopril (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men:women)</td>
<td>31:5</td>
<td>30:3</td>
<td>30:6</td>
</tr>
<tr>
<td>Age (y)*</td>
<td>60 (8-4)</td>
<td>60 (6-11)</td>
<td>60 (3-9)</td>
</tr>
<tr>
<td>Site of infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior:inferior</td>
<td>14 (21)</td>
<td>15 (18)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Receiving thrombolysis</td>
<td>30</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Time to thrombolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(h)*</td>
<td>3 (1-7)</td>
<td>2 (9-9)</td>
<td>3 (2-9)</td>
</tr>
<tr>
<td>Peak creatine kinase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(U)*</td>
<td>1496 (1152)</td>
<td>1333 (975)</td>
<td>1496 (1178)</td>
</tr>
<tr>
<td>Completing trial</td>
<td>27</td>
<td>29</td>
<td>31</td>
</tr>
</tbody>
</table>

*Continuous variables presented as mean (SD).
Table 2 Reasons for not completing trial treatment

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo</th>
<th>Mononitrate</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent withdrawn</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Indigestion</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

No patient appears more than once in this table.

Radionuclide ventriculography

Imaging was performed on 88 patients. Of these five were excluded from analysis because of previous infarction. The 17 patients that were not imaged had similar baseline characteristics to the remaining 88 patients except that they had a shorter duration of trial treatment due to withdrawal or death.

The left ventricular ejection fraction at five weeks was similar in the three groups (fig 2). The captopril group, however, had fewer patients with low ejection fractions (<20%).

Magnetic resonance imaging

Fifty six patients underwent magnetic resonance imaging, the number being limited by availability of the machine and periods when it was out of service. Four studies were discarded due to poor image quality and three abandoned due to claustrophobia. The remaining 49 patients had good quality images that were assessed.

Treatment with vasodilator made no significant difference to the five week end diastolic left ventricular volumes (fig 3).

Clinical outcome

This is an important part of the assessment of the trial as patients who were withdrawn within the first week of the study do not appear in the data on ventricular size and function. Table 4 shows the distribution of patients with an adverse outcome. This analysis was based on an intention to treat and as a history of myocardial infarction would influence outcome, such

Table 3 Difference in mean left ventricular diameter between one and five weeks after infarction (cm)

<table>
<thead>
<tr>
<th></th>
<th>End diastole</th>
<th>End systole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.25 ± 0.15 to 0.65</td>
<td>0.05 ± 0.60 to -0.50</td>
</tr>
<tr>
<td>Mononitrate</td>
<td>0.10 ± 0.35 to -0.50</td>
<td>-0.10 ± 0.2 to -0.48</td>
</tr>
<tr>
<td>Captopril</td>
<td>0.25 ± 0.15 to -0.55</td>
<td>-0.15 ± 0.15 to -0.50</td>
</tr>
</tbody>
</table>

Differences and 95% CI calculated by Mann-Whitney U test.

Patients have been excluded. Two men died and a further two men were withdrawn with cardiogenic shock in the placebo group. These last two patients had ejection fractions measured independently of this study and both were less than 20% (16% and 19%). Also there was one patient in the isosorbide group who died with cardiogenic shock. These patients missing from the left ventricular analysis are a potential source of bias and should be borne in mind when interpreting the results. It is of interest that no patient in the captopril group had such an adverse outcome. The difference in the clinical outcome between the captopril and placebo group was statistically significant (p < 0.05).

Discussion

This study has shown no significant improvement in objective measures of left ventricular function.
ventricular size and function from early vasodilator treatment. Captopril, however, may reduce the number of patients with an adverse clinical outcome. This result contrasts with other published studies reporting the beneficial effect of captopril and nitrates after infarction. In three of these studies no patient received thrombolysis and in the fourth study patients treated with thrombolytic agents were included only if there was a Q wave infarction. Also a two hospital study from Glasgow has recently reported that captopril treatment started within 24 hours of infarction significantly inhibited ventricular dilatation. This study was of similar size to our own but once again this beneficial effect was seen in a population excluding those treated by thrombolysis.

Ventricular dilatation or remodelling has been extensively studied in patients with myocardial infarction not treated by thrombolysis. The proportion of infarctions that result in dilatation depends on the nature of the population studied. Previous work has shown that between 28% and 40% of patients with acute transmural myocardial infarction will undergo ventricular dilatation over the next six months. The major risk factors for dilatation are transmural infarction, anterior infarction, extensive myocardial necrosis and persistent occlusion of the infarct related artery. The particular importance of coronary artery patency in preventing dilatation has been shown in several studies. In one study failure to spontaneously reperfuse the infarct related artery proved to be a more important predictor of dilatation than infarct size. Conversely, decreasing ventricular size after infarction was associated with a patent infarct related coronary artery. A second paper describes 78 patients with acute myocardial infarction, some of whom received thrombolysis. Left ventricular function was better in those patients with a patent artery either induced by thrombolysis or by spontaneous reperfusion. Some of the larger trials of thrombolytic treatment have shown that patency of the infarct related artery is associated with lower long-term mortality. Thrombolysis may have a beneficial effect on ventricular remodelling directly through myocardial salvage. In animal studies, however, late reperfusion without myocardial salvage has been shown to inhibit infarct zone expansion and result in thicker scar tissue. This may explain why some studies, for example the second international study of the infarct survival (ISIS-2), have shown benefit of late thrombolytic treatment.

In our study the placebo group showed no tendency to ventricular dilatation as the ventricular diameter tended to fall over the four week period. This contrasts with the outcome in the placebo groups of the studies by Sharpe et al and Pfeffer et al. We believe that our study shows that in most patients receiving thrombolysis there is little tendency to remodelling and that vasodilator treatment does not produce major benefits in terms of ventricular size and function. Despite this, vasodilator drugs may have an important role in patients who are at increased risk of infarct expansion and dilatation. This is borne out from the adverse clinical outcome in our placebo group. Indeed even Pfeffer et al could only report a significant benefit from captopril treatment in those high risk patients with an occluded infarct related artery.

Our study is small and therefore of limited statistical power. It does, however, show an important finding that should be considered in designing larger studies to assess the role of vasodilator treatment. All patients admitted to a coronary care unit may not benefit from this type of treatment; in particular, those at low risk of ventricular dilatation with small infarcts, inferior territory necrosis, and with patent infarct related coronary arteries.

We thank Ms F Taddei for technical assistance and Mrs V Campbell for secretarial skills. The drug treatment and patient randomization was provided by the ISIS Office, Oxford, as part of the ISIS-4 pilot study and was funded by Bristol-Myers Squibb, who manufacture captopril (Capoten). Isosorbide mononitrate (Monit) was donated by Stuart Pharmaceuticals. The study was conducted, analysed, and interpreted independently of the companies.


<table>
<thead>
<tr>
<th>Placebo</th>
<th>Isosorbide mononitrate</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 29)</td>
<td>(n = 29)</td>
<td>(n = 29)</td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Placebo vs captopril, p < 0.05 (χ²).* No patient appears more than once in this table. All patients with previous myocardial infarction had been excluded. Cardiogenic shock is defined as prolonged hypotension with impairment of perfusion of vital organs without evidence of right ventricular infarction.
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