The effect of angiotensin converting enzyme inhibition on myocardial function and blood pressure after coronary artery bypass surgery—a randomised study

Carolyn M. Webb a, Richard Underwood b, Constantinos Anagnostopoulos b, J. Graeme Bennett c, John Pepper c, Christopher Lincoln c, Peter Collins a,*

a Division of Cardiac Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, Dovehouse Street, London SW2 6LY, UK
b Department of Nuclear Medicine, Royal Brompton Hospital, London, UK
c Department of Cardiothoracic Surgery, Imperial College School of Medicine at the National Heart and Lung Institute, Royal Brompton Hospital, London, UK

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Abstract

Objectives: To investigate the effect of 6 weeks’ pre-operative treatment with the angiotensin converting enzyme inhibitor, quinapril, on left ventricular function when measured 3 months after coronary artery bypass graft surgery and to examine the safety of such treatment. Patients and methods: Patients (96) (86 males, 10 females; mean age 61 years) with chronic stable angina, on the waiting list for coronary artery bypass graft surgery, underwent measurement of left ventricular function by resting radionuclide ventriculography. Patients were then randomised to quinapril 20 mg once daily or placebo in a double-blind fashion, in addition to existing anti-anginal therapy and this regimen was continued for up to 6 weeks prior to operation. Measurement of left ventricular function was repeated 3 months following surgery, after recommencement of pre-surgery anti-anginal therapy for 1 week. Effects on systemic vascular resistance (SVR) during bypass were calculated from perfusion records and vasoconstrictor use during operation was documented. The safety of the addition of quinapril to the anti-anginal regimen was assessed by measurement of systemic blood pressure (BP) after the first dose of study medication, measurement of intra-operative BP, administration of inotropes and any intra-operative complications. Results: There was no difference between treatment groups in the pre-study left ventricular ejection fraction (mean (S.D.); 54.9 (13.8)% versus 55.6 (13.2)%; quinapril versus placebo, respectively), or 3 months after surgery (58.1 (13.6)% versus 56.9 (12.6)%; quinapril versus placebo, respectively). Left ventricular ejection fraction 3 months after surgery did not change significantly from pre-treatment in either group (2.8 (10.7)% and 1.5 (10.1)%; quinapril and placebo, respectively). There was no first-dose hypotension (systolic BP < 100 mmHg). The intra-operative BP and the SVR during bypass in the two treatment groups were not significantly different. The ischaemic time (mean = 56 min) and the use of inotropes were the same in both groups and there was no mortality. Conclusions: Angiotensin converting enzyme inhibitor treatment before coronary artery bypass graft surgery does not have a significant beneficial effect on left ventricular function following coronary artery bypass graft surgery. Angiotensin converting enzyme inhibition, administered in addition to anti-anginal therapy, does not cause first-dose hypotension or increase morbidity or mortality and can safely be used in patients with coronary heart disease prior to coronary artery bypass graft surgery. © 1998 Elsevier Science B.V.

Keywords: Angiotensin converting enzyme-inhibitors; Revascularisation; Left ventricular function; Blood pressure

* Corresponding author. Tel.: +44 171 3518112; fax: +44 171 8233392.

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1. Introduction

Coronary artery bypass grafting is an accepted and widely used method of treating patients with coronary artery disease (CAD), relieving angina in over 85% of cases [1,2]. Conflicting data exist on the effect of coronary artery bypass graft surgery on left ventricular function, with studies showing improvement, no change or deterioration [3–5]. Left ventricular function is a potent predictor of patient survival for patients with CAD [6] and is also a major determinant of prognosis after coronary artery bypass graft surgery [2]. In the coronary artery surgery study (CASS) improvement in survival achieved by surgical revascularisation occurred primarily in patients with impaired left ventricular function [7]. Improvement of left ventricular function following coronary artery bypass graft surgery may, therefore, beneficially affect postoperative morbidity and mortality.

There have been no studies to assess the effect of drug therapy on left ventricular function before and after coronary artery bypass graft surgery. Angiotensin converting enzyme inhibitors are accepted therapies for hypertension and heart failure, have been shown to improve myocardial function in patients with heart failure [8,9] and after myocardial infarction [10–15] and, therefore, could have a beneficial effect in improving left ventricular function after coronary artery bypass graft surgery. Experimental data show that angiotensin converting enzyme inhibition can reduce infarct size in dogs [16]. In this study captopril increased regional myocardial blood flow in the area of infarction, decreased mean arterial pressure and decreased left atrial pressure. Animals treated with captopril had smaller infarct size compared to placebo-treated animals. The favourable action of captopril was attributed to the increase in perfusion of ischaemic tissues as well as to the reduction in pre-load and after-load. Angiotensin converting enzyme inhibitors may, therefore, offer a cardioprotective effect to patients who experience a myocardial ischaemic event whilst taking the drug.

Discrete episodes of ischaemia which are insufficient to jeopardise the viability of the tissue may impair myocardial function permanently or for as long as myocardial perfusion is inadequate. The improvement of left ventricular function after coronary artery bypass graft surgery may be improved further by angiotensin converting enzyme inhibition which is started before operation. Datasheets on angiotensin converting enzyme inhibitors call for caution in patients on angiotensin converting enzyme inhibitors undergoing major surgery with regard to peri- and post-operative hypotension. Therefore, the purpose of this study was 2-fold; firstly to investigate the effect of pre-operative treatment with quinapril (a non-sulphhydryl containing angiotensin converting enzyme inhibitor) on left ventricular function before and after patients underwent coronary artery bypass graft surgery and secondly to examine the effect on blood pressure (BP) and SVR during cardiopulmonary bypass and the safety of such treatment.

2. Patients and methods

2.1. Patients

Patients with chronic stable angina (with no myocardial infarction within the previous 6 months) and not currently taking an angiotensin converting enzyme inhibitor were recruited from the routine list for coronary artery bypass graft surgery at the Royal Brompton Hospital. Patients were included only if they were having first-time coronary artery bypass graft surgery with no underlying valvar or congenital heart disease. Written informed consent was obtained from all patients, following the Royal Brompton Hospital Ethics Committee guidelines. Medical history, physical examination and routine blood tests were performed.

2.2. Study design

Left ventricular function (left ventricular ejection fraction (%)) was measured by a resting radionuclide ventriculogram. Eligible patients were then randomised to receive an angiotensin converting enzyme inhibitor, quinapril 20 mg once daily (Accupro, Parke Davis) or placebo in a double-blind fashion, in addition to existing anti-anginal therapy. The study treatment was continued for up to 6 weeks prior to operation, with the final day of treatment being the morning of surgery. After recommencement of pre-operative anti-anginal therapy for 1 week, left ventricular function assessment was repeated 3 months following surgery. Cardioprotection used during surgery was dependent on the surgeon; either blood cardioplegia via the perfusion pump or St. Thomas’ crystalloid via the aortic root and hypothermia to 20–32°C.

2.3. Left ventricular function measurement

Equilibrium radionuclide ventriculography was performed following in vivo erythrocyte labelling with 740 MBq technetium-99m pertechnetate. A large field of view γ camera (Sopha Medical, Buc, France; model DS7) was used with a low energy all purpose collimator to acquire a 16 frame ventriculogram in a left anterior oblique projection optimised for best separation of the left and right ventricles and with 15° of caudal tilt. Electrocardiographic gating was used with rejection of cycles following one with an RR interval outside 15% of the mean. Acquisition was terminated at a total of 5 million counts. The left ventricle was identified auto-
matically using the end diastolic, end systolic, phase and amplitude images, with manual correction if necessary. Background activity was estimated as 95% of the lowest pixel within the end diastolic region of interest. Left ventricular ejection fraction was calculated from the background corrected activity-time curve generated from the raw image data.

2.4. Assessment of safety

The first dose of study medication was administered in hospital and systemic BP was measured at half-hourly intervals for 2 h for detection of first-dose hypotension (systolic BP < 100 mmHg). Patients suffering first-dose hypotension were excluded from the study. Arterial BP was monitored constantly throughout and following surgery. For analysis we documented the first four BPs after induction of anaesthesia (baseline), first four BPs immediately after cessation of bypass (post-bypass) and first four hourly BPs in the intensive care unit (ITU). The four recordings at each stage were then averaged. Details of number and type of grafts, administration of inotropes and vasoconstrictors and any intra-operative complications were documented.

2.5. Systemic vascular resistance during cardiopulmonary bypass

Mean arterial and venous BPs and pump flow data were documented every 10 min on bypass to allow for calculation of systemic vascular resistance (SVR) during cardiopulmonary bypass. SVR was calculated using the formula: $\text{SVR} = \left( \frac{(\text{mean arterial pressure} - \text{central venous pressure})}{\text{cardiac output (pump flow)}} \right) \times 80$ [17].

SVR was plotted against time for each patient and the slopes of the regression lines were analysed using ANOVA. Vasoconstrictors used during surgery were documented.

2.6. Statistical analysis

Statistical analysis was carried out using the SAS statistical package. Efficacy data was analysed using analysis of covariance (ANCOVA). Intra-operative BPs and systemic vascular resistance were analysed using analysis of variance (ANOVA). $P \leq 0.05$ as considered statistically significant.

3. Results

3.1. Patients

Normotensive patients (96) (86 males, 10 females; mean age 61 years) were randomised to treatment and their characteristics are described in Table 1. Patient 1 had one diseased coronary artery (placebo), 21 patients had two-vessel disease (7 quinapril, 14 placebo) and 74 patients had three-vessel disease (40 quinapril, 34 placebo). Of these patients, 83 completed revascularisation whilst enrolled in the study and 79 completed the study. All patients completed assessment of left ventricular function by resting radionuclide ventriculography. Patients (12) (7 quinapril, 5 placebo) were withdrawn because their study medication ran out before surgery could be performed and 1 patient was withdrawn due to hypotension before the study medication was administered. Therefore, 83 patients (75 males, 8 females; mean age 61 years) were included in efficacy analysis. A further 4 patients withdrew during the 3 month follow-up period for personal reasons and post surgery left ventricular ejection fraction assessments are not available for these patients.

3.2. Left ventricular function

There was no difference between treatment groups in the pre-study left ventricular ejection fraction (mean (S.D.); 54.9 (13.8)% versus 55.6 (13.2)%, quinapril versus placebo, respectively), or 3 months after surgery (58.1 (13.6)% versus 56.9 (12.6)%, quinapril versus placebo, respectively). Left ventricular ejection fraction 3 months after surgery did not change significantly from pre-treatment in either group (2.8 (10.7)% versus 1.5 (10.1)%; quinapril versus placebo, respectively). Patients (7) had baseline left ventricular ejection fraction $\leq 35\%$. The changes in left ventricular ejection fraction in quinapril treated patients (+29%, +22%, +7%) compared to placebo (+14%, +11%, 0%, −8%) demonstrated a trend towards a post-operative

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quinapril ($n = 47$)</th>
<th>Placebo ($n = 49$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Range</td>
<td>44–78</td>
<td>39–77</td>
</tr>
<tr>
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<td>43</td>
</tr>
<tr>
<td>Female</td>
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<td>6</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mean duration of angina (years)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Range</td>
<td>0.2–27</td>
<td>0.4–24</td>
</tr>
<tr>
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<td>17</td>
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<tr>
<td>Previous PTCA</td>
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</tr>
<tr>
<td>Concomitant anti-anginal Rx</td>
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<td></td>
</tr>
<tr>
<td>B-blocker</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Long-term nitrate</td>
<td>28</td>
<td>35</td>
</tr>
</tbody>
</table>
improvement in left ventricular ejection fraction, however, this was not statistically significant.

### 3.3. Assessment of safety

There was no first-dose hypotension. Patients (65) had complete records of intra-operative and immediate post-operative BP readings (30 patients on quinapril and 35 patients on placebo; Table 2). There was no difference in BP between quinapril and placebo at baseline or immediately after bypass. However, there was a significant difference between groups in systolic and mean BP in ITU ($P < 0.05$). There was no significant difference between treatment groups in the requirement of inotropes (Table 3). The surgical complications are presented in Fig. 1. The ischaemic time was the same in both groups (range, 19–117 min; quinapril mean, 57 min; placebo mean, 56 min) and there was no significant difference in the number of grafts applied or length of stay in ITU (Figs. 2 and 3, respectively).

### 3.4. Systemic vascular resistance during cardiopulmonary bypass

There was no difference in SVR during bypass at any time point in the 82 patients with evaluable data. The trend in SVR over time was not significantly different in the treatment groups. The mean slope of the regression lines for patients receiving quinapril was $-2.01$ and for patients receiving placebo was $-2.08$ ($P = 0.94$). There was no difference in the use of vasoconstrictors during surgery between treatment groups.

### Table 3

<table>
<thead>
<tr>
<th>Inotropic support</th>
<th>Quinapril</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
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<td>23</td>
</tr>
<tr>
<td>1</td>
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<td>14</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
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</tr>
<tr>
<td>3</td>
<td>1</td>
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</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
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</table>

All $P = NS$.

### 4. Discussion

In the present study, left ventricular function 3 months after surgery was unaffected by the addition of an angiotensin converting enzyme inhibitor to pre-operative anti-anginal therapy. Angiotensin converting enzyme inhibitor treatment tended to have a more beneficial effect in the group of patients with left ventricular ejection fraction $\leq 35\%$, although the number of patients in this group was too small to demonstrate a significant effect. In the CONSENSUS-I study [8], patients with NYHA class IV given enalapril after anterior myocardial infarction demonstrated a favourable effect on left ventricular dilatation during a 1-year follow-up. The CASS study [7] demonstrated an improvement in survival achieved by surgical revascularisation, occurring primarily in patients with impaired left ventricular function. Patients with impairment of left ventricular function pre-operatively may, therefore, gain more benefit from administration of pre-operative angiotensin converting enzyme inhibitor treatment than those with normal left ventricular function. The majority of patients enrolled in this study had normal pre-operative ejection fraction and this may explain the negative result with regard to left ventricular function. The preservation on myocardial function after surgery may also reflect the choice of myocardial preservation used during surgery; the type of cardioprotection used and the mean ischaemic times did not differ between treatment groups.
The angiotensin converting enzyme inhibitor was administered before the ischaemic event (i.e. surgery) in the present study, whereas, in all the studies of angiotensin converting enzyme inhibition in myocardial infarction and heart failure the angiotensin converting enzyme inhibitor was by definition given after the ischaemic event, or after the development of heart failure. Similarly, by giving an angiotensin converting enzyme inhibitor before surgery we were attempting to attenuate potential peri-operative myocardial damage regardless of pre-operative left ventricular function.

We have demonstrated that angiotensin converting enzyme inhibition may be used safely before coronary artery bypass graft surgery in conjunction with other anti-anginal drugs. This statement is based on our finding that there was no difference in incidence of hypotension during cardiac anaesthesia in patients randomised to either quinapril or placebo, no difference in ischaemic time during surgery and no difference in mortality. In the immediate post-operative hours the quinapril treated group had lower systemic BP, but there was no difference between treatment groups in the requirement of inotropic support or post-operative outcome.

Myocardial ischaemia activates the renin-angiotensin system, which results in increased production of the potent vasoconstrictor and positive inotrope, angiotensin-II, via the conversion of angiotensin-I by angiotensin converting enzyme. Increased angiotensin-II levels may thus further the imbalance between oxygen supply and demand during myocardial ischaemia. Inhibiting the conversion of angiotensin-I to angiotensin-II with an angiotensin converting enzyme inhibitor may, therefore, be beneficial to patients when administered soon after an ischaemic event. A causative relationship has been suggested between angiotensin-II levels and vasoconstriction during non-pulsatile cardiopulmonary bypass. Peripheral vascular resistance has been observed to increase progressively during the perfusion period of operation and persists for the first few hours of the post-operative period, an effect which may be due to effects on the renin-angiotensin system. Cardiopulmonary bypass increases plasma renin levels and activity [18,19], increase angiotensin-I [18] and angiotensin-II levels in animals [20]. Similar results have been demonstrated in humans, where a highly significant correlation was shown between increases in peripheral vascular resistance index and angiotensin-II levels during cardiopulmonary bypass [21]. Treatment with an angiotensin converting enzyme inhibitor 2 h after bypass in dogs has been shown to decrease peripheral vascular resistance index and angiotensin-II levels compared to control animals [22]. Angiotensin-II specifically reduces subendocardial blood flow [23]. This, together with the potent vasoconstrictor action of angiotensin-II, may tend to reduce left ventricular function. Specific angiotensin-II blockade by angiotensin converting enzyme inhibition may, therefore, be cardioprotective via blockade of coronary vasoconstriction, enhancing myocardial perfusion in addition to reducing after-load. However, in the present study no significant rise in SVR with time on bypass was demonstrated in either treatment group. Angiotensin levels were not measured.

The important haemodynamic effects of angiotensin converting enzyme inhibitors have been comprehensively investigated, mainly with captopril [10–16,24]. Ertl et al. [16] reported a potent effect of angiotensin converting enzyme inhibition on reduction of infarct size in dogs after coronary occlusion and hypothesised that this was due to increased collateral flow to the ischaemic zone and reduction of after-load. Captopril exerted a reduction in myocardial damage in a pig model after coronary occlusion then reperfusion for 1 h [24]. The mechanism of myocardial protection by captopril versus placebo was investigated in humans, added to cardioplegia solution during coronary artery bypass graft surgery [25]. Blood samples taken throughout the surgical procedure demonstrated no difference in adrenaline levels but a significant decrease in noradrenaline and creatinine kinase and a non-significant increase in angiotensin-I levels in patients given capto-
pril. The latter suggests blockade of angiotensin converting enzyme and a decrease in angiotensin-II levels. Since local or systemic angiotensin-II influences coronary vascular tone and coronary flow, decreasing angiotensin-II levels might favour dilatation of the coronary vascular bed and enhance myocardial perfusion.

Other angiotensin converting enzyme inhibitors have been developed and with them other mechanisms have become evident. Quinapril, used in the present study and ramipril differ from captopril in that they do not contain a sulphydryl group. Van Gilst et al. [26] investigated the effect of ramipril, in comparison to captopril, on the coronary circulation of isolated rat hearts. Both agents increased coronary flow compared to saline, but captopril increased flow more than ramipril, both in rate of onset and magnitude. Ramipril, however, increased prostacyclin synthesis, an effect which has been confirmed in other studies [27]. This suggests that different molecular structures of angiotensin converting enzyme inhibitors may act by different mechanisms. Other proposed mechanisms for the myocardial protective effect of angiotensin converting enzyme inhibitor include potentiation of bradykinin [28], which may assist in the anti-remodelling effect of angiotensin converting enzyme inhibition after myocardial infarction [29]. Protection may also be due, in part, to suggested anti-oxidant properties of the sulphydryl-containing compounds [29].

Although the present study failed to demonstrate a significant improvement in left ventricular function with pre-operative quinapril treatment, we have demonstrated the safety of such therapy. The trend towards a more favourable effect on post-operative left ventricular function in patients with pre-operative impairment of left ventricular function may be an indication that such patients would benefit from angiotensin converting enzyme inhibition prior to coronary artery bypass graft surgery, however, this hypothesis requires further investigation in patients with a pre-operative left ventricular ejection fraction less than 35%. The results from this study would also suggest that angiotensin converting enzyme inhibitors may safely be used in patients undergoing major surgery other than coronary artery bypass graft surgery.

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References


