ACE inhibition with ramipril improves left ventricular function at rest and post exercise in patients with stable ischaemic heart disease and preserved left ventricular systolic function

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Aims To assess the effects of 6 months intervention with ramipril on resting and post exercise left ventricular function in patients with stable ischaemic heart disease and preserved left ventricular systolic function.

Methods and Results Patients (n=98, age 65±9 years, 37% women) were randomized to double-blind treatment with ramipril 5 mg · day⁻¹ (n=32), ramipril 1·25 mg · day⁻¹ (n=34), or placebo (n=32). Resting and post maximum exercise echocardiography/Doppler examinations were performed at baseline and after 6 months. Changes over 6 months in resting transmitral E-wave deceleration time (Edt) and Edt adjusted for heart rate (Edt/RR) differed between the ramipril 5 mg, ramipril 1·25 mg, and placebo groups: Edt 24±82, 22±61, and 29±64 ms, respectively, P=0·012; Edt/RR 30±105, 25±61, and 28±69 ms, respectively, P=0·015. Changes in the difference between resting and post exercise Edt/RR also varied between groups: −53±137, −28±118, and 35±101 ms, respectively, P=0·029. No differences in E/A indices were noted. Resting atrioventricular plane displacement improved in the combined ramipril groups vs the placebo group: 0·2±0·8 vs −0·2±1·3 mm, P<0·05.

Conclusion Six months ramipril treatment in patients with stable ischaemic heart disease and preserved left ventricular systolic function improved resting left ventricular function and reduced the exercise induced diastolic filling abnormalities usually seen in these patients.

Key Words: Angiotensin converting enzyme inhibitor, ischaemic heart disease, left ventricular function, diastolic function, exercise.

Introduction

Angiotensin-converting enzyme (ACE) is a key enzyme in the pathophysiology of ischaemic heart disease through its effect on the levels of angiotensin II, bradykinin, and nitric oxide. Angiotensin II is a potent vasoconstrictor that induces growth of myocardial and vascular cells as well as increased deposition of collagen, leading to vascular and myocardial remodelling[1]. Conversely, nitric oxide inhibits proliferation of vascular smooth muscle cells[2-4] and is imperative to the relaxation of the vasculature[4]. Angiotensin II, furthermore, exhibits acute effects on left ventricular function, and in experimental studies angiotensin II caused a marked deterioration of left ventricular diastolic dysfunction[5].

In addition, angiotensin II increases PAI-1 and thereby impairs fibrinolytic activity[6-7], whereas bradykinin inhibits platelet aggregation[8-9] and increases tissue type plasminogen activator, leading to improved fibrinolytic capacity[10,11].

An ACE inhibitor may counteract the negative effects of angiotensin II and potentiate the beneficial effects of bradykinin and nitric oxide[12]. Experimentally, ACE inhibition has been shown to attenuate the diastolic dysfunction caused by infusion of angiotensin I, and to blunt the diastolic dysfunction induced by myocardial ischaemia[5]. The progressive remodelling of the myocardium and vascular system, resulting from activation of the renin angiotensin system, is partly inhibited by ACE inhibition[13-17], further supporting the hypothesis that inhibition of the renin angiotensin system is beneficial in patients with ischaemic heart disease.

Whether these effects are of clinical importance in patients with stable ischaemic heart disease is currently
under investigation in several large mortality and morbidity trials\(^{[10]}\). So far, beneficial effects of ACE inhibitors on clinical end-points in patients with ischaemic heart disease have been shown most convincingly in those with left ventricular systolic dysfunction\(^{[10–23]}\), although there is some indication of a beneficial effect also in patients with preserved left ventricular systolic function\(^{[23–31]}\).

The present study was a substudy of the LORAMI (Low dose Ramipril Against Myocardial Ischaemia) study. LORAMI was performed to investigate the effects on myocardial ischaemia of a 6 month intervention with \(1.25\) mg and \(5\) mg \(\text{day}^{-1}\) of the ACE inhibitor ramipril in comparison with placebo, in patients with stable ischaemic heart disease and preserved left ventricular systolic function. A total of 391 consecutive patients were randomized to double-blind treatment. The main efficacy variable was total ischaemic burden (total area of significant ST depression) on a 48 h ambulatory long-term ECG registration. The results of the main study have not yet been published. We chose to include a low dose of ramipril (1.25 mg) in order to test the hypothesis that a dose not a higher dose would still decrease myocardial ischaemia. This was based on findings in experimental\(^{[32]}\) and clinical\(^{[33]}\) studies of an anti-remodelling effect of low, non-antihypertensive doses of ramipril.

The present study aimed to examine any effects of this intervention on left ventricular diastolic filling at rest and post exercise. We also aimed to examine the effects on left ventricular function as assessed by determination of the left atrioventricular plane displacement at rest\(^{[34–39]}\).

**Methods**

**Patients**

Patients 30 to 80 years old, with stable ischaemic heart disease, as judged by a history of myocardial infarction or typical angina pectoris with positive exercise test and/or a pathological coronary angiogram, were examined by ambulatory ECG. Those who showed at least 10 min ST depression of at least 0.1 mV over 48 h were eligible for inclusion. Thus, also patients who had silent ischaemia were eligible. Patients were excluded if they had symptomatic heart failure and/or left ventricular systolic dysfunction constituting an indication for angiotensin converting enzyme (ACE) inhibition, a contra-indication to ACE inhibitor treatment, current ACE inhibitor treatment, inconclusive ambulatory ECG, and unstable angina. Patients thus identified were included in the LORAMI study, and 98 of these patients were randomly included in the present substudy. All patients gave written informed consent to the study, which was approved by the local ethics committee.

**Intervention**

Patients were randomized on a 1:1:1 basis to receive double-blind treatment with either daily ramipril 5 mg, ramipril 1.25 mg, or placebo, in addition to the baseline medication. The intervention started immediately after the baseline examinations and lasted for 24 weeks whereafter the baseline examinations were repeated.

**Echocardiographic examination**

Two-dimensional echocardiography and Doppler examinations were performed using a Hewlett-Packard (Andover, Mass, U.S.A.) Sonos 1000 echocardiography system and a 2.5 MHz transducer. Pulsed, continuous and colour-flow Doppler examinations were performed with the same transducer. Parasternal and apical views were obtained with the patient in a left lateral recumbent position. Measurements were acquired during silent respiration or end-expiratory apnoea.

Left ventricular systolic function was assessed by determination of the mean left atrioventricular plane displacement\(^{[34–39]}\), derived from four measurements at each of the anterior, septal, lateral, and posterior walls (in the four and two chamber views). Left atrioventricular plane displacement can be determined despite poor image quality and shows high reproducibility. The mean inter-observer variability in our laboratory between two investigators examining each patient immediately after one another was 4.8\% (atrioventricular plane displacement difference range 0–1.2 mm) in a series of 53 consecutive patients with a mean left atrioventricular plane displacement of \(7.8\) mm (range \(3.3–15.5\) mm)\(^{[35]}\). The intra-observer variability of the determination of left atrioventricular plane displacement was mean 2.0\% (range 0–6\%), corresponding to 0.23 mm (range 0–0.95 mm), in 39 randomly examined patients with a mean left atrioventricular plane displacement of \(11.2\) mm (range \(5.6–17.5\) mm)\(^{[36]}\). The average left atrioventricular plane displacement in 15 controls (mean age 65 years, range 54 to 77 years, 8 (53\%) women) was \(13.5 \pm 1.1\) mm, and a mean displacement \(\geq 10.0\) mm is considered normal\(^{[37]}\). This method is therefore particularly well suited for assessment of changes in left ventricular function over time. Furthermore, left atrioventricular plane displacement has a very strong prognostic value in patients with heart failure\(^{[38,39]}\).

Cardiac dimensions were measured in the parasternal long axis view in two-dimensional mode\(^{[41,42]}\), Grading of valvular regurgitation was based on colour Doppler signal area, continuous Doppler signal density, and continuous Doppler pressure half time (aortic regurgitation only), from grade 0 to 3.

Left ventricular diastolic performance was evaluated by pulsed Doppler echocardiography as described previously\(^{[43–45]}\), by determination of the early (E) to atrial (A) peak velocity (E/A) and time–velocity integral (E/A) of diastolic transmitral flow. We also measured the time from peak to end of the E-waves; E-deceleration time (Edt). A short Edt is considered to be a measure of impaired diastolic performance with high filling pressure\(^{[46]}\). In our laboratory the mean inter-observer variability of the determination of
Table 1 Baseline age, sex, anthropometrics, and background diseases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ramipril 5 mg (n=32)</th>
<th>Ramipril 1.25 mg (n=34)</th>
<th>Ramipril any dose (n=66)</th>
<th>Placebo (n=32)</th>
<th>Three group P</th>
<th>P ramipril vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 8</td>
<td>64 ± 9</td>
<td>65 ± 9</td>
<td>66 ± 10</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>30</td>
<td>32</td>
<td>31</td>
<td>48</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>171 ± 10</td>
<td>171 ± 9</td>
<td>171 ± 9</td>
<td>168 ± 8</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76 ± 12</td>
<td>75 ± 10</td>
<td>76 ± 11</td>
<td>71 ± 14</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Body surface (m²)</td>
<td>1.89 ± 0.20</td>
<td>1.88 ± 0.18</td>
<td>1.88 ± 0.19</td>
<td>1.80 ± 0.20</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>9</td>
<td>35</td>
<td>23</td>
<td>22</td>
<td>0.041</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9</td>
<td>15</td>
<td>12</td>
<td>6</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac surgery (%)</td>
<td>56</td>
<td>41</td>
<td>48</td>
<td>41</td>
<td>0.053</td>
<td>0.028</td>
</tr>
<tr>
<td>Symptomatic stable angina (%)</td>
<td>88</td>
<td>82</td>
<td>85</td>
<td>100</td>
<td>0.003</td>
<td>ns</td>
</tr>
<tr>
<td>Prior unstable angina (%)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Prior atrial fibrillation (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Prior myocardial infarction (%)</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>50</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Edt was 9% (range 0–59 ms) and the intra-observer variability was 5.4% (range 0–30 ms) in 30 patients with Edt between 130 and 410 ms. Evaluation of diastolic performance was done at rest as well as approximately 10 min following a maximum exercise test, as soon as the patients’ respiration had returned to normal. Exercise-induced myocardial ischaemia affects left ventricular filling, assessed by transmitral Doppler, up to at least 2 h following an exercise test. In patients with ischaemic heart disease the E/Amax decreases, whereas the Edt increases following an exercise test, in comparison with the resting situation. Patients with a left atrioventricular plane displacement corresponding to an ejection fraction of 45% or less were excluded from the post-exercise examination because the Doppler indices in these patients were judged likely to be substantially affected by alterations in systolic function post exercise.

All measurements were performed blindly and all analyses of measurements were pre-determined before the code was broken.

**Exercise testing**

The exercise tests were at both baseline and study end performed in the morning, fasting or at least 3 h after a light breakfast, using upright bicycle ergometry, and were limited by exhaustion or chest pain. The initial work load of 30 to 50 W was increased stepwise by 10 W every minute. Continuous 12-lead ECG registration with computerized ST analysis was performed, as well as blood pressure measurement, registration of effort, chest pain, and dyspnoea according to the Borg scale every second minute.

**Statistics**

The t-test was used to test differences between two groups. For three group comparisons the Kruskal-Wallis test was performed. When comparing nominal variables between two groups a chi-squared or, where appropriate, Fisher’s exact test was used. Data are expressed as mean (SD). Two-tailed P values <0.05 were considered significant.

**Results**

All 98 patients were examined by echocardiography at rest at both baseline and following the 24 week intervention period. At baseline six patients had a left atrioventricular plane displacement corresponding to a left ventricular ejection fraction of 45% or less, and were, according to protocol, excluded from the post-exercise evaluation. Thus left ventricular diastolic performance post exercise was assessed in 92 patients at both baseline and study end. Age, sex, anthropometrics, and background diseases are shown in Table 1. There was significant difference between the three treatment groups regarding a history of hypertension, but overall there was no difference between all ramipril-treated patients and those receiving placebo. There was a borderline-significant difference between the three treatment groups regarding the frequency of symptomatic angina, and comparing all patients receiving ramipril with those on placebo this difference was significant. There were no differences between the three treatment groups with respect to baseline medication. Although three patients in the placebo group had a history of atrial fibrillation, all patients were in sinus rhythm during the study period.

**Baseline Doppler variables**

Baseline Doppler variables of left ventricular diastolic filling at rest were similar in the three treatment groups and comparing all patients on ramipril to the placebo group (Table 2). Differences between rest and post-
Table 2  Baseline echocardiographic and transmitral Doppler variables at rest. There were no significant differences between groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ramipril 5 mg</th>
<th>Ramipril 1/25 mg</th>
<th>Ramipril any dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDd/m² (mm)</td>
<td>26 ± 3 7</td>
<td>27 ± 0 2 5</td>
<td>33 ± 0 2 1</td>
<td>60 ± 2 8</td>
</tr>
<tr>
<td>LVIDs/m² (mm)</td>
<td>6 8 ± 1 3</td>
<td>28 ± 0 7 2</td>
<td>32 ± 0 7 2</td>
<td>60 ± 5 9</td>
</tr>
<tr>
<td>LVPWDd/m² (mm)</td>
<td>3 8 ± 1 0</td>
<td>27 ± 0 1 0</td>
<td>33 ± 0 2 0</td>
<td>60 ± 5 4</td>
</tr>
<tr>
<td>LAs/m² (mm)</td>
<td>21 7 ± 2 9</td>
<td>29 ± 2 2 4</td>
<td>33 ± 2 2 1</td>
<td>62 ± 2 3</td>
</tr>
<tr>
<td>MR degree</td>
<td>1 0 ± 0 5</td>
<td>32 ± 0 9 0 ± 5</td>
<td>34 ± 1 0 0 5</td>
<td>66 ± 1 1</td>
</tr>
<tr>
<td>RVIDd/m² (mm)</td>
<td>15 4 ± 2 1</td>
<td>27 ± 1 4 2 2</td>
<td>33 ± 1 5 2 2</td>
<td>60 ± 5 6</td>
</tr>
<tr>
<td>mean AVPD (mm)</td>
<td>1 2 0 ± 1 9</td>
<td>32 ± 0 2 0 2 1</td>
<td>34 ± 1 2 0 5 0</td>
<td>66 ± 1 2</td>
</tr>
<tr>
<td>E/Amax</td>
<td>1 9 ± 0 5 4</td>
<td>32 ± 1 2 4 ± 0 58</td>
<td>34 ± 1 2 1 ± 0 56</td>
<td>66 ± 1 1 1 ± 0 4 ± 2 2</td>
</tr>
<tr>
<td>E/Aintegral</td>
<td>1 6 8 ± 1 0 1</td>
<td>32 ± 2 0 ± 1 5 4</td>
<td>33 ± 1 8 5 ± 1 3 0</td>
<td>65 ± 1 7 8 ± 0 8 8 2</td>
</tr>
<tr>
<td>Edt (ms)</td>
<td>23 1 ± 5 5</td>
<td>32 ± 2 4 9 ± 6 5</td>
<td>34 ± 2 4 0 ± 6 0 6</td>
<td>66 ± 2 5 8 ± 5 5</td>
</tr>
<tr>
<td>Edt/RR (ms)</td>
<td>23 4 ± 5 7</td>
<td>32 ± 2 4 5 ± 6 7</td>
<td>34 ± 2 4 0 ± 6 2 6</td>
<td>66 ± 2 5 7 ± 7 1 52</td>
</tr>
</tbody>
</table>

AVPD=atrioventricular plane displacement; E/Aintegral=integral of early to atrial transmitral flow; E/Amax=maximum velocity of early to atrial transmitral flow; Edt=deceleration time of early transmitral flow; Edt/RR=deceleration time of early transmitral flow adjusted for RR-interval; LVIDd=interventricular septal diameter at end-diastole; LVIDs=left atrial diameter at end-systole; LVPWDd=left ventricular posterior wall diameter at end-diastole; MR=mitral regurgitation; RVIDd=right ventricular internal diameter at end-diastole.

Table 3  Difference (Δ) between resting and post-exercise transmitral diastolic Doppler variables at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ramipril 5 mg (n=30)</th>
<th>Ramipril 1/25 mg (n=31)</th>
<th>Ramipril any dose (n=61)</th>
<th>Placebo (n=31)</th>
<th>Three group P</th>
<th>P ramipril vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ E/Amax</td>
<td>-0 15 ± 0 29</td>
<td>-0 02 ± 0 28</td>
<td>-0 08 ± 0 29</td>
<td>-0 09 ± 0 19</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Δ E/Aintegral</td>
<td>-0 30 ± 0 68</td>
<td>-0 09 ± 0 94</td>
<td>-0 19 ± 0 83</td>
<td>-0 05 ± 0 53</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Δ Edt (ms)</td>
<td>17 ± 73</td>
<td>13 ± 83</td>
<td>17 ± 76</td>
<td>-17 ± 80</td>
<td>ns</td>
<td>0 048</td>
</tr>
<tr>
<td>Δ Edt/RR (ms)</td>
<td>59 ± 86</td>
<td>50 ± 101</td>
<td>57 ± 92</td>
<td>5 ± 88</td>
<td>ns</td>
<td>0 012</td>
</tr>
</tbody>
</table>

Δ=difference between the value at rest and the value post exercise; E/Aintegral=integral of early to atrial transmitral flow; E/Amax=maximum velocity of early to atrial transmitral flow; Edt=deceleration time of early transmitral flow; Edt/RR=deceleration time of early transmitral flow adjusted for RR-interval.

exercise (Δ) in transmitral Doppler variables at baseline were similar in the three treatment groups (Table 3). However, when all patients on ramipril were compared to the placebo group there were significant differences regarding ΔEdt and ΔEdt/RR (Table 3), indicating less post exercise ischaemia in the placebo group.

Changes from baseline to study end in Doppler variables

There was a significant difference between the three treatment groups regarding change from baseline to study end in Edt and Edt/RR at rest (Table 4, Fig. 1). Thus the ramipril 5 mg group showed an increase in Edt and Edt/RR, whereas the ramipril 1/25 mg group showed no changes, and the placebo group showed a decrease. When comparing all patients on ramipril with the placebo group the same beneficial effect of ramipril was evident (Table 4, Fig. 2). Most ramipril patients with a short Edt at baseline showed Edt prolongation towards normal at study end, whereas ramipril patients with a long baseline Edt showed a shortening towards normal (Fig. 2). The three treatment groups differed significantly with respect to changes from baseline to study end in ΔEdt/RR, and there was a borderline–significant difference regarding ΔEdt (Table 5, Fig. 3), indicating that ramipril attenuated the post exercise increase in Edt. The same benefit was evident comparing all patients on ramipril to the placebo group (Table 5, Fig. 3).

Echocardiographic variables

The three treatment groups were similar regarding all baseline echocardiographic variables at rest (Table 2). There were no differences between the three treatment groups regarding changes from baseline to study end in echocardiographic variables at rest. However, when
comparing all patients on ramipril with the placebo group the changes in mean atrioventricular plane displacement differed significantly between groups (0.2 ± 0.8 mm vs −0.2 ± 1.3 mm, P=0.046), indicating a beneficial effect of ramipril on left ventricular function at rest.

### Discussion

This study shows, for the first time, that ACE inhibition in patients with stable ischaemic heart disease and preserved left ventricular systolic function can improve left ventricular function at rest and attenuate the exercise-induced impairment of left ventricular filling, usually seen as a result myocardial ischaemia.

Differences between treatment groups in Doppler variables of left ventricular diastolic performance were significant for Edt and Edt adjusted for heart rate (Edt/RR) at rest, as well as E/Amax and E/A. Edt is considered one of the most important Doppler measures of left ventricular diastolic performance. In patients with ischaemic heart disease and post exercise myocardial ischaemia Edt increases following an exercise test, in comparison with the resting situation. An improvement of the diastolic performance at exercise would thus attenuate this prolongation of Edt post exercise, as seen in the ramipril-treated patients in the present study.

As indicated in Fig. 2, the average prolongation of resting Edt in patients treated with ramipril most likely was the result of improved diastolic filling in patients with more pronounced baseline filling disturbances. In such patients Edt is shortened, and an improved diastolic performance prolongs Edt towards normal, as seen in the present study in most ramipril-treated patients with shortened baseline resting Edt. A prolonged resting Edt is found in patients with mild diastolic filling abnormalities and relaxation disturbances. An improved diastolic performance shortens the resting Edt towards normal in such patients, as seen in the present study among most ramipril treated patients with

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ramipril 5 mg</th>
<th>n</th>
<th>Ramipril 1·25 mg</th>
<th>n</th>
<th>Ramipril any dose</th>
<th>n</th>
<th>Placebo</th>
<th>n</th>
<th>Three group P</th>
<th>P ramipril vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/Amax (m/s)</td>
<td>0·06 ± 0·41</td>
<td>32</td>
<td>−0·03 ± 0·44</td>
<td>34</td>
<td>0·01 ± 0·42</td>
<td>66</td>
<td>−0·06 ± 0·29</td>
<td>31</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>E/A (m/s)</td>
<td>0·1 ± 0·71</td>
<td>32</td>
<td>−0·10 ± 1·57</td>
<td>33</td>
<td>0·00 ± 1·22</td>
<td>65</td>
<td>−0·20 ± 0·83</td>
<td>31</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Edt (ms)</td>
<td>27 ± 82</td>
<td>32</td>
<td>−1 ± 69</td>
<td>34</td>
<td>11 ± 76</td>
<td>66</td>
<td>−29 ± 64</td>
<td>32</td>
<td>0·019</td>
<td>0·012</td>
</tr>
<tr>
<td>Edt/RR (ms)</td>
<td>30 ± 105</td>
<td>32</td>
<td>2 ± 61</td>
<td>34</td>
<td>16 ± 86</td>
<td>66</td>
<td>−28 ± 69</td>
<td>31</td>
<td>0·049</td>
<td>0·015</td>
</tr>
</tbody>
</table>

E/Aintegral= integral of early to atrial transmitral flow; E/Amax= maximum velocity of early to atrial transmitral flow; Edt= deceleration time of early transmitral flow; Edt/RR= deceleration time of early transmitral flow adjusted for RR-interval.
prolonged baseline resting Edt. Most ramipril patients with intermediate baseline Edt changed very little as a result of the intervention.

The differences found with respect to left ventricular diastolic performance and atioventricular plane displacement were clear and significant although rather small numerically. Regarding Edt and Edt/RR as well as $\Delta$Edt and $\Delta$Edt/RR the results indicate a more pronounced improvement in patients on 5 mg ramipril compared to those on the lower dose, suggesting that a higher dose might be more efficacious than a dose not affecting central haemodynamics.

There is nothing to indicate that the changes from baseline to study end in Doppler variables of left ventricular diastolic performance were due to regression towards the mean. Quite the opposite, the placebo group changed from baseline values indicating less compromised diastolic performance than the ramipril groups, to values indicating more impaired diastolic performance than the ramipril groups at study end. The direction of change in the ramipril groups, especially the ramipril 5 mg group, was the opposite. This was seen with respect to Edt and Edt/RR at rest as well as $\Delta$Edt and $\Delta$Edt/RR.

The treatment groups showed some differences in the baseline variables, which may be potentially important to the interpretation of the results. Thus, there were more patients with symptomatic angina in the placebo group compared to the group of ramipril-treated patients. On the other hand, there were significant differences regarding $\Delta$Edt and $\Delta$Edt/RR comparing all patients on ramipril with the placebo group (Table 3), indicating less post exercise ischaemia in the placebo group. It is therefore difficult to say if there actually were any differences between the treatment groups with regard to myocardial ischaemia at baseline. There was also a difference in the three-group comparison regarding a history of hypertension, which was not seen when all patients on ramipril were compared to the placebo

![Figure 2](image)

Resting Edt (ms) at baseline (X-axis) and study end (Y-axis). The line of identity is indicated. $\times$=ramipril treated patients, $\bigcirc$=placebo treated patients. Edt=deceleration time of early transmitral flow.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ramipril 5 mg n</th>
<th>Ramipril 125 mg n</th>
<th>Ramipril n</th>
<th>Placebo n</th>
<th>Three group $P$</th>
<th>$P$ ramipril vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ E/Amax</td>
<td>0.07 ± 0.43</td>
<td>30</td>
<td>0.00 ± 0.42</td>
<td>31</td>
<td>0.04 ± 0.42</td>
<td>61</td>
</tr>
<tr>
<td>$\Delta$ E/Aintegral</td>
<td>0.16 ± 0.66</td>
<td>30</td>
<td>0.02 ± 0.98</td>
<td>30</td>
<td>0.09 ± 0.83</td>
<td>60</td>
</tr>
<tr>
<td>$\Delta$ Edt (ms)</td>
<td>−37 ± 116</td>
<td>30</td>
<td>−17 ± 113</td>
<td>31</td>
<td>−27 ± 114</td>
<td>61</td>
</tr>
<tr>
<td>$\Delta$ Edt/RR (ms)</td>
<td>−53 ± 137</td>
<td>30</td>
<td>−28 ± 118</td>
<td>31</td>
<td>−40 ± 128</td>
<td>61</td>
</tr>
</tbody>
</table>

$\Delta$=difference between the value at rest and the value post exercise; E/Amax=maximum velocity of early to atrial transmitral flow; E/Aintegral=integral of early to atrial transmitral flow; Edt=deceleration time of early transmitral flow; Edt/RR=deceleration time of early transmitral flow adjusted for RR-interval.

Table 5 Changes from baseline to study end in difference between resting and post-exercise ($\Delta$) transmitral Doppler variables
group. It is unlikely that these differences in the baseline variables have affected the results of the study in a way that changes our conclusions.

The difficulties assessing left ventricular diastolic function by transmitral Doppler evaluation are well recognised. We found no differences between the treatment groups in terms of changes in E/A indices, which may reflect the difficulties separating normal and pseudonormal E/A indices. Transmitral Doppler indices are affected by other factors besides left ventricular diastolic function, such as left ventricular preload, transmitral pressure differences, left ventricular afterload, and left atrial function. It is therefore possible that the observed changes in the Doppler indices of left ventricular filling were not exclusively caused by changes in left ventricular diastolic function. We believe, however, that it is correct to state that the observed changes were caused by improved left ventricular diastolic filling, taking into account all factors that influence diastolic performance.

There are several possible mechanisms by which ACE inhibition may improve left ventricular diastolic performance in patients with ischaemic heart disease[52]. The beneficial effects of ramipril might be due to improved coronary vessel endothelial function as a consequence of decreased levels of angiotensin II and increased levels of bradykinin and nitric oxide[53]. ACE expression and angiotensin II production are increased in atherosclerotic tissue[54]. By inhibiting ACE locally oxidative stress may decrease, causing improved endothelial function and increased myocardium perfusion and oxygen supply. Consequently, the observed beneficial effect of ramipril on diastolic performance may have been caused by improved oxygen supply. Since atrioventricular plane displacement is predominantly related to the function of subendocardial, longitudinal myocardial fibres[38,40], improved perfusion of the subendocardium may also explain the beneficial effect of ramipril on atrioventricular plane displacement. This explanation of our results is supported by the findings of other studies. The TREND study demonstrated an improvement of endothelial vasomotor dysfunction in patients with ischaemic heart disease treated with quinapril over 6 months, and it was indicated that ACE inhibition improved microvascular coronary blood flow[23,55]. Moreover, in a study by Gasic et al.[29], cilazapril improved regional myocardial blood flow to the ischaemic myocardium in patients with stable angina.

Angiotensin II facilitates the release of norepinephrine from sympathetic nerve terminals[56], and ACE inhibitors have been shown to confer parasympathomimetic effects[57–59], improve baroreflex sensitivity in patients after myocardial infarction[60], and reduce sympathetic vasomotor tone in hypertensive patients[61]. Consequently, ACE inhibitor induced reduction of sympathetic activity due to decreased levels of angiotensin II may have contributed to a decrease in myocardial ischaemia and thereby an improvement of left ventricular diastolic performance. The issue of modulating effects on sympathetic activity of ACE inhibition in humans is, however, still controversial[62].

A haemodynamic effect due to decreased pre- and afterload from ACE inhibitor induced vasodilatation may also have contributed to the resulting improved diastolic performance. Any haemodynamic effect might have
been small and the fact that there were no changes in left ventricular or atrial size at rest during follow-up does not preclude such an effect.

An improved neurohormonal balance may have induced a regression of structural myocardial changes such as myocardial fibrosis, in turn improving diastolic compliance. Such an effect may be independent of any haemodynamic effects and attributed to inhibition of cardiac tissue ACE, as seen in experimental studies. Even a modest regression of fibrosis may improve coronary vessel compliance, especially a decrease in perivascular fibrosis. Such a change may improve the coronary reserve, which in particular would cause an attenuation of post exercise ischaemia. However, the study duration may have been too short for such changes to occur. In the SAVE (Survival And Ventricular Enlargement study) and SOLVD (Studies Of Left Ventricular Dysfunction) studies ACE inhibitor effects attributable to structural changes were not seen until after 6 months treatment.

Since several experimental and clinical studies have shown that ACE inhibitors are capable of reducing atherosclerosis, an anti-atherogenic effect may contribute to explain our results. However, ACE inhibitors have shown little success in preventing restenosis after angioplasty in humans, and in the QUIET (Quinapril Ischaemic Event Trial) trial treatment with quinapril after angioplasty failed to reduce mortality and recurrence of angina pectoris in comparison with placebo. Furthermore, the duration of our study may have been too short for any anti-atherogenic effects to develop.

There are no prior reports about the effect of ACE inhibition on left ventricular function in patients with ischaemic heart disease and preserved left ventricular systolic function. In the experimental setting, however, ACE inhibition has been shown to attenuate the diastolic dysfunction caused by myocardial ischaemia. Several studies have shown convincing anti-ischaemic effects of ACE inhibition in patients with left ventricular systolic dysfunction. But anti-ischaemic effects of ACE inhibition have also been shown in patients with ischaemic heart disease and preserved left ventricular systolic function. Furthermore, in hypertensive patients with microvascular angina pectoris, enalapril significantly improved the coronary reserve and reduced clinical manifestations of ischaemia as well as ischaemia at the exercise test.

An anti-ischaemic effect from ACE inhibition in patients with ischaemic heart disease and preserved left ventricular systolic function may very well lead to improved left ventricular function. The observed improvement in atroventricular plane displacement may have been due to improved systolic function of subendocardial fibres, but may also have been caused by improved diastolic function. We have previously shown that moderate to severely compromised left ventricular diastolic performance is associated with decreased atrioventricular plane displacement, independent of systolic function.

Conclusions

In conclusion, a 6-month intervention with ramipril in patients with ischaemic heart disease and preserved left ventricular systolic function induced an improvement in left ventricular diastolic performance post exercise and at rest. The effect of the higher dose of ramipril was more pronounced than that of the lower dose, and did not affect central haemodynamics. In ramipril-treated patients there was also an improvement in left atrioventricular plane displacement, further supporting the finding of an improved left ventricular function as a result of ACE inhibition. Several large ongoing trials are currently investigating the effects of ACE inhibition on mortality and morbidity in patients with stable ischaemic heart disease, and the relevance of our results for the clinical outcome in these patients will soon be known.

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References


