Left ventricular diastolic function and cardiac disease
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Effect of Mibefradil on left ventricular diastolic function in patients with congestive heart failure


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Summary

Background: Calcium antagonists are known to have anti-hypertensive and anti-anginal properties. In heart failure however, their use can be hazardous, as systolic function can deteriorate. This may not be true for the new calcium antagonist Mibefradil, which has a new chemical structure. Calcium antagonists may also be beneficial for diastolic left ventricular function in coronary artery disease. In order to investigate the possible effects of Mibefradil on diastolic left ventricular function we performed the present study in the setting of a multicenter, double blind, placebo controlled, multiple dose, safety trial.

Methods: Fifteen patients with NYHA class II or III for dyspnoea and depressed ejection fraction (<40%) due to a previous myocardial infarction were investigated. The measured nuclear angiographic parameters included Ejection Fraction, Peak Ejection Rate and Peak Filling Rate. Systolic blood pressure, diastolic blood pressure and heart rate were also obtained. Group I (5 patients) received placebo medication, group IIA (6 patients) Mibefradil 6.25, 12.5 or 25 mg daily and group IIB (4 patients) 50 or 100 mg daily. Measurements were made before and after the first dose and after one week of treatment before and after the final dose.

Results: Mibefradil clearly depressed Heart Rate (repeated measures analysis of variance: p<0.05). No statistically significant effects of Mibefradil were measured on blood pressures, systolic and diastolic left ventricular function.

Conclusions: In our study conditions Mibefradil caused no worsening of systolic function and preserved diastolic function in short-term treatment of patients with decreased EF and heart failure.

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As a result of myocardial infarction congestive heart failure can develop. This may be primarily due to diastolic dysfunction, or to a combination of diastolic and systolic dysfunction of the left ventricle. \(1,2,3\) Diastolic dysfunction, in this context, implies that the left ventricle is not able to accept blood at low pressures. \(1,4,5\) Pulmonary congestion can thus develop. \(1,4,5\) The use of calcium antagonists for the treatment of stable angina in such patients can be hazardous because of a potential deterioration of systolic function. \(6,7,8\) This may not necessarily be true in the case of second- and third-generation calcium antagonists, which might in fact benefit diastolic function in coronary artery disease. \(2,8,9\)

Mibefradil, a calcium antagonist from a new chemical structural class of benzimidazolyl-substituted tetraline derivatives, has been found to possess strong anti-anginal properties. \(10\) In addition, no deterioration of systolic function has been reported in patients with chronic stable angina pectoris and also in rats with chronic myocardial infarction. \(10,11\) To date, no reports have occurred concerning the safety of Mibefradil on systolic and diastolic left ventricular function in patients with chronic heart failure. The effects of Mibefradil on diastolic left ventricular function in patients with congestive heart failure due to earlier myocardial infarction were investigated in the present study.

**METHODS**

**Patients.** Fifteen patients with chronic congestive heart failure, NYHA class II or III were included in this study. All patients had suffered myocardial infarction more than three months prior to the investigation, which resulted in a left ventricular ejection fraction of 40 percent or less. Exclusion criteria included: unstable angina pectoris; clinically significant valvar disease, including mitral regurgitation; hypertrophic obstructive or dilated cardiomyopathy; moderate or uncontrolled hypertension; clinically significant arrhythmias or bradycardia and 1st or higher degree AV-block.

**Study design.** On day one of investigation patients were randomised in a double blind design for their study medication, which was either placebo (Group I, five patients) or Mibefradil (Group II, ten patients). Those patients receiving Mibefradil were randomly assigned in pairs to different dose groups. Six patients received Mibefradil in the relatively low doses of 6.25, 12.5 and 25 mg daily (Group IIA). The remaining four patients received the higher doses of 50 and 100 mg Mibefradil daily (Group IIB). They then underwent multigated nuclear angiography at approximately 10 AM. Three hours later (1 PM) a second nuclear angiography was performed. For the following seven days patients received their study medication once daily. On day eight a multigated nuclear angiogram was made before and three hours after ingestion of the last study tablet (10 AM and 1 PM). During nuclear angiography resting systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were also obtained. Mean arterial pressure (MAP) was then calculated.
Nuclear angiography. Some of each patient’s red blood cells were labelled with 99m technetium-pertechnetate, after intravenous administration of stannous pyrophosphate. The total dosage range was 550-740 MBq. Left ventricular function was evaluated by radionuclide angiography using a gamma camera (Siemens Orbiter) with an all-purpose parallel-hole collimator and interfaced with a Pinnacle computer (Medasys Inc, Ann Arbor). Multigated images in supine rest position were obtained in the left anterior oblique view with a caudal tilt, such that both left and right ventricles appeared separated. Only a 5% cycle-length-window with forward gating was accepted. Acquisition was completed after 150,000 counts per frame of 20 ms. Temporal smoothing was achieved using five Fourier harmonics. Measurements. From the systolic part of the left ventricular time-activity curve (TAC) we measured the Ejection Fraction (EF) and the Peak Ejection Rate (PER). The diastolic parameters included the Peak Filling Rate (PFR) and the time to Peak Filling Rate (t-PFR). PFR was normalised to end-diastolic volume as well as stroke volume. Atrial Contribution (AC) was measured as a percentage of the diastolic filling volume.

Statistical analysis. Measured data are expressed as mean ± 1 SD unless otherwise stated. For statistical analysis a model of repeated measures analysis of variance was used since the same variable was obtained on several occasions. In this design the variability due to differences between subjects can be eliminated from the experimental error. A p-value <0.05 was considered statistically significant. We tested the differences in the means with the various Mibefradil dosages. In the case of an immediate effect of Mibefradil on the tested parameters we would expect a third order polynomial for group II. This would be more pronounced in the higher dosage group IIB. In the case of a delayed medication effect we would expect a linear change in the parameters of group II.

RESULTS

Patients. The patients’ baseline characteristics are presented in Table 6.1. All calcium

<table>
<thead>
<tr>
<th>TABLE 6.1. Baseline characteristics of the 15 study patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex male/female</td>
</tr>
<tr>
<td>Functional class</td>
</tr>
<tr>
<td>NYHA II</td>
</tr>
<tr>
<td>NYHA III</td>
</tr>
<tr>
<td>LV ejection fraction</td>
</tr>
<tr>
<td>Location of myocardial infarction*</td>
</tr>
<tr>
<td>Inferoposterior</td>
</tr>
<tr>
<td>Anterior</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Previous interventions</td>
</tr>
<tr>
<td>CABG</td>
</tr>
</tbody>
</table>

* more than one infarction location per patient possible.
CABG = coronary artery bypass graft; NYHA = New York Heart Association; LV = left ventricular.
antagonists and β-blocking agents were withdrawn at least five half-lives before trial. All other oral medication was continued. At baseline there were no statistically significant differences between the three groups.

**Effects of Mibefradil on mean arterial pressure, heart rate and ejection fraction.** Table 6.2 shows the findings on heart rate, mean arterial pressure and ejection fraction. Heart rate was decreased by Mibefradil (p<0.05). This bradycardic effect was evident only after one week of treatment in the high dose group (Figure 6.1). No effect of Mibefradil was seen on SBP, DBP, MAP, EF and PER.

**Effects of Mibefradil on the diastolic nuclear angiographic parameters.** The findings on the diastolic nuclear angiographic parameters are summarised in Table 6.3. Mibefradil had no statistically significant effect on PFR, both when normalised to end-diastolic counts or to stroke counts (Figure 6.2A and 6.2B). Mibefradil had no effect on AC (Figure 6.3) or t-PFR.

**DISCUSSION**

The aim of the present study was to investigate the effects of Mibefradil on diastolic left ventricular function in patients with heart failure and decreased ejection fraction due to previous myocardial infarction. Diastolic function was assessed by measuring various indices of diastole using nuclear angiography (PFR, t-PFR and AC). Several indices of systolic function were also measured using this technique (EF and PER).

The interpretation of diastolic parameters in patients with systolic dysfunction is

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mibefradil (mg/day)</th>
<th>PFR (EDV/s) Day 1 BM</th>
<th>PFR (EDV/s) Day 8 BM</th>
<th>Normalised PFR (SV/s) Day 1 BM</th>
<th>Normalised PFR (SV/s) Day 8 BM</th>
<th>AC (%SV) Day 1 BM</th>
<th>AC (%SV) Day 8 BM</th>
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<td>1</td>
<td>0</td>
<td>0.98 0.92 0.92 1.01</td>
<td>3.8 3.8 3.5 3.9</td>
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<td></td>
<td></td>
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<tr>
<td>2</td>
<td>0</td>
<td>1.51 1.40 1.10 1.61</td>
<td>3.5 2.7 1.9 3.4</td>
<td>29 25 28 20</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>0</td>
<td>0.51 0.70 0.59 0.79</td>
<td>4.0 4.6 3.5 4.6</td>
<td>20 18 19 19</td>
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<tr>
<td>4</td>
<td>0</td>
<td>0.61 0.64 0.72 0.85</td>
<td>2.8 2.7 3.1 3.7</td>
<td>71 44 38 36</td>
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<tr>
<td>5</td>
<td>0</td>
<td>0.39 1.53 0.63 0.94</td>
<td>2.1 6.4 3.3 5.2</td>
<td>65 56 52 76</td>
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<tr>
<td>6</td>
<td>6.25</td>
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<td>2.1 1.7 2.2 2.9</td>
<td>32 37 35 52</td>
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<td>6.25</td>
<td>0.87 1.12 1.15 1.13</td>
<td>3.4 4.3 4.1 4.2</td>
<td>22 27 31 52</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>12.5</td>
<td>1.02 1.17 0.91 1.15</td>
<td>3.0 3.5 2.8 3.1</td>
<td>63 57 53 53</td>
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<tr>
<td>10</td>
<td>25</td>
<td>0.70 0.95 0.84 1.14</td>
<td>3.7 4.1 5.0 4.8</td>
<td>36 26 30 28</td>
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<tr>
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<td>2.0 2.8 2.5 2.1</td>
<td>36 44 52 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>0.78 1.48 0.77 0.66</td>
<td>3.2 5.3 2.3 1.8</td>
<td>58 87 44 47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>1.57 1.28 1.16 1.35</td>
<td>6.3 4.4 5.0 5.4</td>
<td>74 66 56 29</td>
<td></td>
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<tr>
<td>14</td>
<td>100</td>
<td>0.93 0.85 1.10 1.10</td>
<td>2.9 2.5 3.1 2.8</td>
<td>37 34 37 34</td>
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<tr>
<td>15</td>
<td>100</td>
<td>0.50 0.56 0.48 0.65</td>
<td>2.1 2.4 1.8 2.3</td>
<td>27 35 29 23</td>
<td></td>
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</tr>
</tbody>
</table>

PFR = peak filling rate; AC = atrial contribution; EDV = end-diastolic volume; SV = Stroke volume; BM = before medication; AM = three hours after medication.
complex. Not only physiological variations such as heart rate and blood pressure can influence the outcome of measurements on diastolic function, but also methodological aspects such as gating mode and normalisation parameters in radionuclide angiography, must be taken into account when studying diastolic parameters. The interpretation of these parameters must therefore be made with great caution. In standardised situations, however, diastolic parameters in patients with systolic dysfunction are likely to be reproducible.

The data show that Mibefradil had a statistically significant effect on HR, especially in the dosages of 50 and 100 mg daily. No such effect was found at dosages of 6.25 to 100 mg daily on either systolic or diastolic parameters or blood pressure.

In previous studies performed on patients with chronic heart failure adverse reactions of short-term treatment with calcium antagonists on systolic function has been emphasized. The observed systolic deterioration may not however, be present in treatment with second-generation calcium antagonists. These results are in agreement with those of the present study, where no statistically significant effect of Mibefradil on EF and PER was found.

The effect of calcium antagonists in heart failure on diastolic function has not been extensively reported, but a stabilising and beneficial effect has been recorded in several studies. This effect is probably due either to the negative chronotropic or to
Effect of Mibefradil on diastolic LV function in CHF

FIGURE 6.1. Line graph of the heart rate (HR) on day 1 before and 3 hours after medication intake and after 1 week of treatment before and 3 hours after the last medication intake. There is a statistically significant decrease in heart rate as a result of Mibefradil (p<0.05).

FIGURE 6.2A. Line graph of Peak Filling Rate (PFR), normalised to end-diastolic volume (EDV) on day 1 before and 3 hours after medication and after 1 week of treatment before and 3 hours after the last medication intake. Mibefradil had no statistically significant effect on this parameter.

FIGURE 6.2B. Line graph of Peak Filling Rate (PFR'), normalised to stroke volume (SV) on day 1 before and 3 hours after medication and after 1 week of treatment before and 3 hours after the last medication intake. Mibefradil had no statistically significant effect on this parameter.

FIGURE 6.3. Line graph of the Atrial Contribution to diastolic filling (AC) on day 1 before and 3 hours after medication and after 1 week of treatment before and 3 hours after the last medication intake. Mibefradil had no statistical significant effect on this parameter.
the coronary vasodilator properties of calcium antagonists. In the former explanation more time is available to produce increased left ventricular filling whereas by vasodilatation a better balance between myocardial oxygen demand and supply is achieved. This is likely to be an important mechanism in the improvement of diastolic function in patients with coronary artery disease after coronary angioplasty or bypass surgery. It could also be an important mechanism in the improvement of diastolic function after oral calcium antagonists in patients with recent myocardial infarction and depressed left ventricular systolic function. Coronary vasodilatation was also observed in anaesthetised dogs during ischaemia after Mibefradil i.v. Moreover, in stable angina in humans, Mibefradil has proven to be effective in doses of 50, 100 and 200 mg daily. Whether or not vasodilatation plays a role in chronic heart failure due to old myocardial infarction remains uncertain.

In the present data no evidence was found for improvement or worsening of diastolic function after short-term Mibefradil in patients with severely depressed systolic function. This may be due to the relatively low doses in which it was administered. However, no direct effect on PFR was found in group IIB either. The combined data suggest that the short-term administration of the new calcium antagonist Mibefradil is relatively safe in patients with coronary artery disease and depressed left ventricular function. The long-term treatment of patients with heart failure with Mibefradil remains however to be investigated. The mechanism for the unfavourable effects of calcium antagonists in the long-term treatment of patients with heart failure is probably multifactorial. The negative inotropic effect of most calcium antagonists is probably less with Mibefradil. However, the possible role of unfavourable neurohormonal activation in patients with heart failure when treated with Mibefradil is not yet clear. More research is therefore needed on a larger study population at adequate doses for the treatment of angina pectoris to be able to draw more definite conclusions on the safety of Mibefradil in patients with heart failure.

**Conclusion.** Compared to a control group of patients who received placebo medication a clear statistically significant effect of Mibefradil was measured on heart rate, while no effect was measured on blood pressure, systolic and diastolic left ventricular function. We conclude therefore that short-term administration of Mibefradil in patients with heart failure due to previous myocardial infarction is probably safe.

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