Angiotensin-(1–7) Attenuates the Development of Heart Failure After Myocardial Infarction in Rats

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Background—The renin-angiotensin system (RAS) is a key player in the progression of heart failure. Angiotensin-(1–7) is thought to modulate the activity of the RAS. Furthermore, this peptide may play a part in the beneficial effects of angiotensin-converting enzyme inhibitors in cardiovascular disease. We assessed the effects of angiotensin-(1–7) on the progression of heart failure.

Methods and Results—Male Sprague-Dawley rats underwent either coronary ligation or sham surgery. Two weeks after induction of myocardial infarction, intravenous infusion of angiotensin-(1–7) (24 μg/kg per hour) or saline was started by minipump. After 8 weeks of treatment, hemodynamic parameters were measured, endothelial function was assessed in isolated aortic rings, and plasma angiotensin-(1–7) levels were determined. Myocardial infarction resulted in a significant deterioration of left ventricular systolic and diastolic pressure, dP/dt, and coronary flow. Raising plasma levels 40-fold, angiotensin-(1–7) infusion attenuated this impairment to a nonsignificant level, markedly illustrated by a 40% reduction in left ventricular end-diastolic pressure. Furthermore, angiotensin-(1–7) completely preserved aortic endothelial function, whereas endothelium-dependent relaxation in aortas of saline-treated infarcted rats was significantly decreased.

Conclusions—Angiotensin-(1–7) preserved cardiac function, coronary perfusion, and aortic endothelial function in a rat model for heart failure. (Circulation. 2002;105:1548-1550.)

Key Words: angiotensin ■ heart failure ■ hemodynamics ■ myocardial infarction

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Langendorff setup, endothelial function was tested in isolated aortic rings, and plasma Ang-(1–7) levels were measured by radioimmunoassay. In the remainder of the text, the maximal rate of change in ventricular pressure is indicated as dP/dt.

## Histology

Midventricular slices were processed for histochemical analysis. Infarct size was determined on picrosirius red/fast green–stained sections and was expressed as the percentage of risk length of total left ventricular circumference. Rats with infarcts smaller than 20% were excluded (n=3 for Ang-(1–7) and n=1 for saline-treated rats). Capillary density was determined on sections stained with biotin–lectin I (GSL-I) and hematoxylin and was expressed as the number of capillaries per mm². Myocyte cross-sectional area was measured on hematoxylin/eosin-stained sections.

## Statistical Analysis

Data are presented as mean±SEM. Statistical analysis between the groups was performed by 1-way ANOVA followed by Bonferroni’s t test. Differences in dose-response curves were tested by ANOVA for repeated measures with Greenhouse-Geisser correction for asphericity. Differences were considered significant at P<0.05.

## Results

### General Characteristics

General parameters at the end of treatment are shown in Table 1. There was no difference in body weight among the 3 groups. Infarct size did not differ between the Ang-(1–7) and saline-treated group, with an average of 33%. Left ventricular weight to body weight ratios were equally increased in both MI groups compared with sham-operated controls (17% in infarcted rats, but did not differ between the Ang-(1–7) and saline-treated groups.

To confirm delivery of the peptide, Ang-(1–7) plasma levels were measured at the end of treatment. Intravenous infusion of Ang-(1–7) increased plasma levels of the peptide 40-fold compared with MI controls to 917.8±194.1 pmol/L (Table 1).

### Hemodynamics

After 8 weeks of treatment, cardiac function was measured in vivo in anesthetized rats. As expected, cardiac function was significantly impaired in untreated MI rats compared with sham-operated rats. In contrast, in Ang-(1–7)–treated rats, none of these parameters were significantly deteriorated, except the systolic dP/dt.

### Endothelial Function

Endothelial dysfunction is a key feature in heart failure. To examine the effects of Ang-(1–7) treatment on this aspect of cardiac failure, we investigated endothelium-dependent relaxation in isolated aortic rings. Phenylephrine elicited similar contractile responses in all 3 groups (data not shown). The response of aortic rings from infarcted animals to the endothelium-dependent vasodi-

## Table 1. General Characteristics After 8 Weeks of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>MI Control</th>
<th>MI Ang-(1–7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, g</td>
<td>432.9±6.8</td>
<td>418.0±6.1</td>
<td>414.0±9.0</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>...</td>
<td>35.5±2.2</td>
<td>29.6±3.3</td>
</tr>
<tr>
<td>LVW/BW, mg/g</td>
<td>2.88±0.08</td>
<td>3.46±0.14*</td>
<td>3.42±0.10*</td>
</tr>
<tr>
<td>Ang-(1–7), pmol/L</td>
<td>9.9±1.9</td>
<td>22.9±7.8</td>
<td>917.8±194.1††</td>
</tr>
<tr>
<td>Myocyte cross-sectional area</td>
<td>341±17</td>
<td>456±25*</td>
<td>409±21</td>
</tr>
<tr>
<td>Capillary density, N/mm²</td>
<td>3104±142</td>
<td>2531±179*</td>
<td>2578±176*</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SEM. BW indicates body weight; LVW/BW, left ventricular weight/body weight ratio; and Ang-(1–7), plasma concentration of angiotensin-(1–7).

*P<0.05 vs sham; †P<0.05 vs MI control.

## Table 2. Ex Vivo Coronary Flow

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>MI Control</th>
<th>MI Ang-(1–7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.7±0.6</td>
<td>6.8±0.3*</td>
<td>8.2±0.6</td>
</tr>
<tr>
<td>Bradykinin 3×10⁻⁸ mol/L</td>
<td>12.1±0.6</td>
<td>9.9±0.4*</td>
<td>11.1±0.7</td>
</tr>
<tr>
<td>Adenosine 10⁻⁵ mol/L</td>
<td>14.0±0.5</td>
<td>10.8±0.5*</td>
<td>12.3±0.8</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SEM in mL/min per gram ventricular weight.

*P<0.05.
latter metacholine was markedly impaired and was lowered to 58.4% (±11.7%) of the response of aortic rings from sham-operated rats (P<0.05, MI control vs sham; Figure 2). In Ang-(1–7)–treated rats, however, metacholine-induced relaxation was identical to sham rats (P<0.05 versus MI control; Figure 2). The relaxation in response to the endothelium-independent vasodilator NaN03 (10–2 mol/L) was equal in the 3 groups (data not shown).

Discussion

In the present study, the effects of intravenous infusion of Ang-(1–7) on the development of heart failure were examined in a rat coronary artery ligation model. We found that 8 weeks of Ang-(1–7) treatment prevented the deterioration of cardiac function, as shown by a 40% reduction in left ventricular end-diastolic pressure, an almost full preservation of coronary flow, and preserved aortic endothelial function. Although Ang-(1–7) has weak vasodilator activities,10 an increase in mean arterial pressure was found in the group infused with Ang-(1–7). Moreover, myocyte hypertrophy was attenuated by Ang-(1–7) infusion. Both results may be indicative of an intracardiac mode of action for Ang-(1–7). A putative local effect of Ang-(1–7) would be in line with a previous study,17 in which 12 days of Ang-(1–7) infusion was found to inhibit restenosis after balloon-catheter injury of carotid arteries.

Interestingly, infusing Ang-(1–7) to levels obtained with ACE inhibition yields similar beneficial effects, including reduction of left ventricular end-diastolic pressure,15 preservation of aortic endothelial function,14,18 improvement of coronary flow,14 and reduction of myocyte hypertrophy.19 On the other hand, differences seem to exist between Ang-(1–7) infusion and ACE inhibition. ACE inhibitors fail to exhibit a positive effect on left ventricular systolic pressure and lower blood pressure even further,20 whereas Ang-(1–7) augments left ventricular systolic pressure and mean arterial pressure. In addition, Ang-(1–7), unlike ACE inhibitors,20 did not improve capillary density. The similarity between Ang-(1–7) infusion and ACE inhibitor treatment may be explained by the fact that ACE inhibitors increase Ang-(1–7) levels. Further, Ang-(1–7), like ACE inhibitors, potentiates bradykinin by acting as an ACE inhibitor,2 which may contribute to similar therapeutic effects of these compounds in cardiac failure. This study shows that Ang-(1–7) is an effective agent in the attenuation of the development of heart failure after MI.

Acknowledgment

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References

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