Renin Inhibition Improves Cardiac Function and Remodeling After Myocardial Infarction Independent of Blood Pressure

Dirk Westermann, Alexander Riad, Olga Lettau, Anton Roks, Konstantinos Savvatis, Peter Moritz Becher, Felicitas Escher, A.H. Jan Danser, Heinz-Peter Schultheiss, Carsten Tschope

Abstract—Pharmacological renin inhibition with aliskiren is an effective antihypertensive drug treatment, but it is currently unknown whether aliskiren is able to attenuate cardiac failure independent of its blood pressure–lowering effects. We investigated the effect of aliskiren on cardiac remodeling, apoptosis, and left ventricular (LV) function after experimental myocardial infarction (MI). C57J/bl6 mice were subjected to coronary artery ligation and were treated for 10 days with vehicle or aliskiren (50 mg/kg per day via an SC osmopump), whereas sham-operated animals served as controls. This dose of aliskiren, which did not affect systemic blood pressure, improved systolic and diastolic LV function, as measured by the assessment of pressure-volume loops after MI. Furthermore, after MI LV dilatation, cardiac hypertrophy and lung weights were decreased in mice treated with aliskiren compared with placebo-treated mice after MI. This was associated with a normalization of the mitogen-activated protein kinase P38 and extracellular signal-regulated kinases 1/2, AKT, and the apoptotic markers bax and bcl-2 (all measured by Western blots), as well as the number of TUNEL-positive cells in histology. LV dilatation, as well as the associated upregulation of gene expression (mRNA abundance) and activity (by zymography) of the cardiac metalloproteinase 9 in the placebo group after MI, was also attenuated in the aliskiren-treated group. Aliskiren improved LV dysfunction after MI in a dose that did not affect blood pressure. This was associated with the amelioration of cardiac remodelling, hypertrophy, and apoptosis. (Hypertension. 2008;52:1068-1075.)

Key Words: aliskiren ■ renin inhibitor ■ myocardial infarction ■ cardiac remodeling ■ matrix metalloproteinase

The renin-angiotensin system (RAS) is activated after myocardial infarction (MI). This increased RAS activity plays a key role in the development of cardiac failure by stimulating (via its effector peptide angiotensin II), alongside other matters, cardiac hypertrophy, apoptosis, and left ventricular (LV) dilatation, all known to contribute to an increased morbidity and mortality in patients with post-MI heart failure. A prevention of this adverse cardiac remodeling, which depresses cardiac function after MI, remains one of the most important pharmacological targets in treating post-MI patients. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been proven to be effective in attenuating the progress of cardiovascular remodeling by inhibiting the increased RAS activity, but nonetheless, they may not effectively inhibit the RAS and thereby antagonize disease progression in all patients.1 Therefore, other potent drugs inhibiting the RAS were studied, and direct renin inhibitors were created. Because renin is the rate-limiting step in angiotensin II production, it has been argued that direct renin inhibitors are more efficient RAS inhibitors than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Moreover, increased renin activity was shown to be a risk factor for MI in hypertensive patients.2 The renin inhibitor aliskiren, a novel drug for RAS inhibition, was shown to reduce blood pressure in patients with arterial hypertension.3 This blood pressure–lowering effect was associated with increased end organ protection in the kidney and the heart, as shown in different animal models.4–6 Moreover, in recent animal models it was shown that development of atherosclerosis in low-density lipoprotein receptor knockout mice was reduced,7 and plaque vulnerability8 was improved by aliskiren treatment. However, whether renin inhibition prevents cardiac failure independent of blood pressure has not yet been investigated. We hypothesized that renin inhibition improves LV function and cardiac remodeling after MI independently from blood pressure and investigated the effect of a subpressor dose of aliskiren on LV function and remodeling after experimental MI in mice.
**Table 1. Blood Pressure Changes Because of Different Doses of Aliskiren**

<table>
<thead>
<tr>
<th>Parameters Studied</th>
<th>CO</th>
<th>Aliskiren 10 mg</th>
<th>Aliskiren 50 mg</th>
<th>Aliskiren 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>109±6</td>
<td>105±4</td>
<td>107±4</td>
<td>88±5*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75±4</td>
<td>72±5</td>
<td>68±5</td>
<td>45±7*</td>
</tr>
</tbody>
</table>

Data are means±SEMs. Data are the results of the pilot study undertaken to obtain a non–blood pressure-lowering dose of aliskiren. It was only treatment with 100 mg/kg of body weight that significantly lowered systolic and diastolic blood pressures.

*P<0.05 vs CO.

**Methods**

For details of the methods please see the online data supplement available at http://hyper.ahajournals.org.

**Animals and Experimental Protocol**

Seventy male C57bl6 mice, aged 10 to 12 weeks, were used in the current study. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health and was approved by the local ethics committee.

**Histological Assessment of Apoptosis by TUNEL Staining**

In cryosections we detected apoptotic cells by end labeling the fragmented DNA using the DeadEnd Colorimetric TUNEL System (Promega) according to the manufacturer’s instructions.

**Real-Time RT-PCR**

Real-time RT-PCR was carried out as described previously using primers (Applied Biosystems) for the matrix metalloproteinase (MMP) 9, as well as their tissue inhibitor (TIMP) 1, tumor necrosis factor-α, collagen type 1, and collagen type 3.

**Immunohistological Measurements**

Immunohistochemistry was carried out using primary antibodies (TIMP-1, collagen type 1, and collagen type 3; Chemicon), followed by the DAKO Envision horseradish peroxidase technique (DAKO). All of the stained sections (sham LV, scar tissue, and noninfarcted septum) were quantified by digital image analysis. Moreover, myocyte cross-sectional area was calculated.

**Western Blot**

LV samples of the noninfarcted region of the heart were homogenized in lysis buffer containing proteinase and phosphatase inhibitors. The total and the phosphorylated forms of the mitogen-activated protein (MAP) kinases P38, extracellular signal-regulated kinase (ERK) 1/2, and AKT were detected with each specific antibody (all from Cell Signaling Technology). Furthermore, calcineurin, bax, bcl-2, GAPDH (all from Cell Signaling Technology), and MMP-13 (2 bands at 60 and at 48 kDa; Dianova) were detected.

**Zymography of MMP-9 Activity**

Gelatin zymography was performed to determine gelatinolytic activities of MMP-9 as described in detail recently using scar tissue of the MI animals.

**Statistical Analysis**

Statistical analysis was performed using SPSS 13.0 (SPSS, Inc). Data are expressed as the means±SEMs. Statistical differences were assessed by using the Kruskal-Wallis test in conjunction with the Mann-Whitney U test. Differences were considered to be statistically significant at a value of P<0.05.

**Table 2. Animal Characteristics**

<table>
<thead>
<tr>
<th>Parameters Studied</th>
<th>Sham</th>
<th>Sham Aliskiren</th>
<th>MI</th>
<th>MI Aliskiren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>25±2</td>
<td>24±1</td>
<td>22±2</td>
<td>23±3</td>
</tr>
<tr>
<td>Heart weight, mg/kg of body weight</td>
<td>98±8</td>
<td>103±6</td>
<td>158±13*</td>
<td>123±9†</td>
</tr>
<tr>
<td>Myocyte cross-sectional area, μm²</td>
<td>148±6</td>
<td>152±9</td>
<td>196±14*</td>
<td>174±11†</td>
</tr>
<tr>
<td>Lung weight, wet/dry</td>
<td>4.2±0.3</td>
<td>4.5±0.5</td>
<td>6.9±0.9*</td>
<td>5.3±0.6†</td>
</tr>
</tbody>
</table>

Data are means±SEMs. The heart weight was increased 10 days after MI in the placebo-treated animals, a finding that was attenuated by aliskiren treatment.

*P<0.05 vs sham.
†P<0.05 vs MI.

**Results**

**Blood Pressure**

To obtain a dose of aliskiren that had a significant effect on blood pressure, we investigated the blood pressure levels of mice treated with 3 different dosages of aliskiren. Only at the highest dose (100 mg/kg of body weight) was blood pressure significantly lower than that in placebo-treated animals. No statistically significant lowering of the blood pressure was documented at the other doses (10 and 50 mg/kg of body weight). Therefore, in the following MI study, 50 mg/kg of body weight was used (Table 1). Coherently, blood pressure was not decreased after MI in this study compared with placebo-treated animals.

**Cardiac Function**

The sham-operated animals did not show any differences in cardiac systolic and diastolic functions when the placebo-treated sham animals were compared with aliskiren-treated sham animals. Ten days after induction of MI, we observed a decrease in systolic and diastolic functions in the placebo-treated MI animals. LV pressure, as well as contractility (dP/dt max), was decreased compared with those values of sham animals. Diastolic function was seen to be aggravated with increased LV end diastolic pressure and relaxation (dP/dt min). Furthermore, cardiac dilatation was documented with an increase in end systolic and diastolic volumes. Decreased stroke volume and ejection fraction, as well as cardiac output, were decreased compared with sham animals. Treatment with aliskiren increased cardiac systolic function (LV pressure, dP/dt max) and diastolic function (LV end diastolic pressure, dP/dt min) and was found to be potent to decrease cardiac dilatation, which finally improved cardiac output. Moreover, load-independent values of systolic and diastolic parameters were also improved (end systolic elastance and stiffness). End systolic elastance, as a parameter of cardiac contractility, and stiffness, as a parameter for LV compliance, are important because they describe cardiac function more independent of the actual load situation of the LV. Furthermore, the ratio of wet lung weight:dry lung weight was increased after MI in the placebo group, and this was improved by aliskiren treatment (Tables 2 and 3).

**Cardiac Apoptosis**

The activation state of the MAP kinase ERK 1/2 was significantly decreased in the myocardial tissue of the MI...
group compared with shams. Aliskiren treatment normalized the phosphorylation state when MI-aliskiren was compared with MI and the sham controls. Furthermore, we observed a downregulation of the MAP kinase p38 phosphorylation state in the myocardium of the untreated animals after MI, which was also normalized by aliskiren treatment. As an indicator of proapoptotic mechanisms, we measured the ratio of bax:bcl-2 and found an increase of this ratio in the placebo MI animals. Again, this was normalized by aliskiren treatment, when MI and MI-aliskiren were compared. These changes were accompanied by an increase in the TUNEL-positive cells measured in the MI area (Figure 1). Most TUNEL-positive cells were fibroblasts or invading cells; only few cardiomyocytes were TUNEL positive 10 days after induction of MI.

### Table 3. Blood Pressure and Cardiac Function

<table>
<thead>
<tr>
<th>Parameters Studied</th>
<th>Sham</th>
<th>Sham Aliskiren</th>
<th>MI</th>
<th>MI Aliskiren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>104±4</td>
<td>101±3</td>
<td>78±6*</td>
<td>86±5†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>68±3</td>
<td>65±4</td>
<td>55±4*</td>
<td>62±4†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>456±18</td>
<td>445±22</td>
<td>475±27</td>
<td>489±23</td>
</tr>
<tr>
<td>Volume end diastolic, µL</td>
<td>54±3</td>
<td>57±2</td>
<td>82±4*</td>
<td>68±5†</td>
</tr>
<tr>
<td>Volume end systolic, µL</td>
<td>22±3</td>
<td>19±3</td>
<td>66±5*</td>
<td>44±3†</td>
</tr>
<tr>
<td>Stroke volume, µL</td>
<td>30±4</td>
<td>33±5</td>
<td>16±5*</td>
<td>23±5†</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>13.6±0.5</td>
<td>14.2±0.7</td>
<td>7.6±1.1*</td>
<td>11.1±1.2†</td>
</tr>
<tr>
<td>LV systolic pressure, mm Hg</td>
<td>106±4</td>
<td>104±5</td>
<td>78±5*</td>
<td>89±6†</td>
</tr>
<tr>
<td>dP/dt max, mm Hg/s</td>
<td>7125±235</td>
<td>6987±358</td>
<td>4125±458*</td>
<td>5254±286†</td>
</tr>
<tr>
<td>EF, %</td>
<td>61±5</td>
<td>63±6</td>
<td>22±5*</td>
<td>35±5†</td>
</tr>
<tr>
<td>LV diastolic pressure, mm Hg</td>
<td>1.1±0.3</td>
<td>1.8±0.5</td>
<td>12±3.4*</td>
<td>8.8±4†</td>
</tr>
<tr>
<td>dP/dt min, mm Hg/s</td>
<td>−6254±213</td>
<td>−6077±268</td>
<td>−3133±358*</td>
<td>−4125±188†</td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>1.88±0.3</td>
<td>1.79±0.4</td>
<td>1.13±0.4*</td>
<td>1.49±0.5†</td>
</tr>
<tr>
<td>Diastolic stiffness, mL⁻¹</td>
<td>0.027±0.004</td>
<td>0.019±0.006</td>
<td>0.130±0.02*</td>
<td>0.09±0.02†</td>
</tr>
</tbody>
</table>

Data are means±SEMs. Hemodynamic parameters were measured by conductance catheter 10 days after induction of MI or sham. EF indicates ejection fraction; Ees, end systolic elastance.

*P<0.05 vs sham placebo.
†P<0.05 vs MI placebo.

Figure 1. A, The ratio of bax:bcl-2 was determined, and an increased proapoptotic pathway was documented in the MI-placebo group. Aliskiren treatment normalized the bax:bcl-2 ratio compared with shams. B, Furthermore, histological stainings with representative pictures revealed an increase in TUNEL-positive cells in the scar of the MI-placebo group compared with the scar of the MI-aliskiren group. C, Moreover, the gene expression of tumor necrosis factor-α was increased after MI and significantly downregulated in the non-infarcted septum of the MI-aliskiren group. *P<0.05 vs MI-aliskiren; &P<0.05 vs MI septum; #P<0.05 vs MI septum aliskiren; ¥P<0.05 vs sham placebo and sham aliskiren.
Cardiac Hypertrophy

Cardiac hypertrophy was observed 10 days after MI in the placebo-treated group compared with sham-operated animals. This was attenuated in the aliskiren-treated MI group compared with placebo-treated MI. Coherently, the myocyte cross-sectional area was increased in the placebo-treated animals compared with the aliskiren-treated animals post-MI (Table 2). These changes were associated with an increase of the AKT activation state, as measured by increased phosphorylated to total AKT in the placebo group. This was attenuated by treatment with aliskiren, when MI to MI-aliskiren comparisons were made. Calcineurin levels were not seen to be different between any of the groups (Figure 2).

Cardiac Changes in the Extracellular Matrix

MI increased the gene expression of MMP-9 in the placebo-treated groups, when the MI area was compared with the non-MI area. This upregulation was normalized by treatment with aliskiren. In contrast, the TIMP-1 expression was increased in both groups, when the MI area was compared with non-MI area, but this increment of TIMP-1 gene expression was even more pronounced in the aliskiren-treated MI group when compared with the placebo-treated group. Furthermore, we analyzed the collagen accumulation in the cardiac tissue. Collagen type 1 and 3 mRNA abundance, as well as protein levels by histochemistry, were increased in the MI area of the animals in both groups and only not statistically decreased by aliskiren treatment (Figure 3). Coherently, the major cardiac collagenase, MMP-13, was downregulated in the MI animals with no statistical difference between MI placebo and MI aliskiren (Figure 4). Moreover, tumor necrosis factor-α gene expression was decreased in the noninfarcted septum in the aliskiren-treated animals compared with the placebo-treated animals but only nonstatistically reduced in the scar tissue.

Cardiac Renin Levels

Aliskiren added during the renin measurement inhibited cardiac angiotensin I generation by 99.9 ± 0.2%, and, thus, all of the cardiac angiotensin I–generating activity detected in our assay could be attributed to renin. Cardiac renin was unaltered after MI. Aliskiren treatment upregulated cardiac renin both in control and MI animals (Figure 5).

Discussion

The salient finding of the current study is that renin inhibition with a subpressor dose of aliskiren improves LV function and
cardiac remodeling after experimental MI in mice. Pharmacological inhibition of the RAS using the renin inhibitor aliskiren was shown to lower blood pressure in humans with arterial hypertension. Blood pressure lowering with aliskiren also reduced end organ damage, as shown by different animal studies. In this study, we investigated potential effects of aliskiren on cardiac failure and not on hypertensive end organ damage; therefore, we used nontransgenic mice, which harbor normal murine renin. For this reason, we had to use higher doses in comparison with those studies investigating the effect of aliskiren in humans or the human renin transgenic rat. Nevertheless, we used a dose that was not blood pressure lowering in normotensive Bl6/C57 mice, in agreement with data by others. After chronic in vivo treatment with aliskiren, an increase of cardiac renin activity was observed (Figure 5). This increase can be attributed to the well-known upregulation of renal renin during RAS blockade, combined with the fact that cardiac renin is kidney derived, even under pathophysiological conditions. It, thus, confirms that aliskiren highly effectively blocked the RAS. The fact that a rise in cardiac renin could be detected at all during aliskiren treatment at first sight implies that aliskiren did not reach cardiac tissue sites in sufficient quantities to block the upregulated cardiac renin levels. However, this is highly unlikely given the cardioprotective effects of aliskiren observed in this study. A more likely explanation, also in view of the low affinity of aliskiren for mouse renin, is that the tissue homogenization procedure and/or the subsequent acidification and dilution before the measurement of angiotensin I generation in vitro have uncoupled the renin-aliskiren complex, thus allowing the quantification of renin by enzyme-kinetic assay in cardiac homogenates despite the in vivo treatment with aliskiren. This observation has been made before. Notably, the addition of aliskiren at a high concentration of 10 μmol/L during the in vitro assay completely inhibited angiotensin I formation. This shows that the measured angiotensin I–generating activity is fully dependent on renin.

In the current study, aliskiren improved LV dysfunction and was accompanied by decreased LV dilatation and hypertrophy after MI in mice. These results suggest that renin inhibition is potent in attenuating the cardioprotective effects of angiotensin II–induced pathology, which occur during cardiac failure. Angiotensin II is known to stimulate different intracellular pathways, and, thus, it might be a potent stimulus of adverse cardiac remodeling by affecting, among other things, the MAP kinases ERK 1/2 and p38. The regulation of those kinases after MI, which is a highly dynamic state, will contribute to many different pathological changes like, eg, apoptosis, hypertrophy, and cardiac fibrosis.

ERK 1/2 activation is known to be protective in cardiac ischemia reperfusion injury, an effect that is at least in part attributed to its antiapoptotic effects. Although the role and the relevance of apoptosis in ischemic heart failure are still
unclear, it was suggested that increased apoptosis contributes to cardiac remodeling after experimental MI. Coherently, we demonstrate downregulation of ERK 1/2 activation 10 days after MI, which is associated with an increased ratio of bax:bcl-2, known to promote cardiac apoptosis. Renin inhibition could normalize both. Furthermore, this was accompanied by a decreased number of TUNEL-positive cells undergoing apoptosis in the infarcted area.

The role of the MAP kinase p38 is debated in ischemic heart failure. Evidence exists that p38 activation worsens the outcome of ischemia reperfusion injury, and, thus, studies have shown, eg, that p38 inhibition during short-term ischemia can indeed be beneficial and cardioprotective. Nevertheless, others showed that p38 inhibition had no effect here, when permanent coronary ligation was used and treatment was started 1 week after induction of MI, and it was suggested that the possible beneficial role of p38 inhibition might be limited to an early time point after MI. Less data exist about the regulation of p38 in the later phases of MI. It was shown recently that, 2 weeks after induction of MI p38 activation is decreased and that experimental intensification of p38 by adenovector-mediated gene transfer rescues cardiac function after experimental MI. Our data are in line with these findings, because we also documented a downregulation of the p38 activation 10 days after MI, which was normalized by aliskiren treatment. Those authors concluded that decreased p38 activation is a possible mechanism in the development of post-MI heart failure and showed, moreover, that, comparable to our findings, apoptosis was reduced after p38 reactivation.

Cardiac hypertrophy increases mortality in patients with heart failure, and prevention of the compensatory hypertrophy after MI is beneficial. We found a marked hypertrophy in placebo-treated animals, which was associated with an increase in AKT but not in calcineurin. It is known that RAS inhibition, when angiotensin-converting enzyme inhibition or angiotensin receptor blockers are used, is potent to reduce that compensatory hypertrophy. Coherently, treatment with aliskiren was able to attenuate this hypertrophy and normalize the activation state of AKT in our study.

**Figure 4.** Gene expression measured by real-time RT-PCR of MMP-9 (A) and TIMP-1 (B). Ten days after MI, the gene expression of MMP-9 was increased in the scar of the placebo-treated MI animals. This increment was normalized by aliskiren treatment. Furthermore, gene expression of TIMP-1 was increased after MI, but this was more pronounced in the aliskiren-treated animals. The MMP-9 activity (measured by zymography, see representative blot) was increased in the scar area of the placebo animals compared with the aliskiren-treated animals, whereas the protein content of TIMP-1 in the scar was increased by aliskiren treatment. D, Representative pictures for TIMP-1. *P<0.05 vs MI scar aliskiren; &P<0.05 vs MI scar aliskiren and MI septum placebo.

**Figure 5.** Cardiac renin levels in sham and MI animals with and without aliskiren treatment. Renin concentrations were measured by enzyme-kinetic assay and have been expressed as nanograms of angiotensin (ANG) I per milligram of protein per hour. Aliskiren, when added at a high concentration of 10 μmol/L during the assay, completely inhibited angiotensin I–generating activity (data not shown). This suggests that all angiotensin I–generating activity was because of renin. Data are means±SEMs (n=3 to 10). *P<0.05 vs sham placebo; &P<0.05 vs MI placebo.
Cardiac collagen stabilizes the scar tissue post-MI and may prevent cardiac rupture in the early phase after MI.\(^2\) In this study, aliskiren did not alter the accumulation of collagen in the scar. On the other hand, excessive accumulation of cardiac collagen in the non-MI area may also impair contractile function long after MI. MMP-13, the major rodent collagenase, was downregulated in placebo and aliskiren-treated animals 10 days after MI compared with their sham-operated controls. Together with the increased mRNA of collagen types I and III of both groups, protein levels of collagen I and III were increased in the scar of placebo and aliskiren-treated animals. This increment was not statistically different between the aliskiren and placebo-treated groups. Because the regulation of cardiac collagen accumulation is highly time dependent after MI, future studies have to evaluate whether aliskiren alters cardiac collagen levels when higher doses or later time points after MI are investigated. This time dependence might also explain that mRNA levels of collagen type 1 and 3 only were increased in the remote myocardium, whereas the protein levels were not significantly different from shams.

Another mechanism leading to heart failure after MI is subsequent cardiac dilatation and infarct thinning (also termed “infarct expansion”) which may lead to development of aneurysm and LV rupture. It was shown that MMP-9 is important for this cardiac dilatation,\(^23\) as well as for the invasion of inflammatory cells.\(^24\) Coherently, it was shown that changes in the MMP system and development of LV hypertrophy are associated with the transition from compensated to decompensated heart failure.\(^25,26\) MMP-9, which is, furthermore, an important biomarker for post-MI dilatation,\(^27\) especially increases the risk of LV rupture and, therefore, its genetic deletion attenuated post-MI mortality.\(^28\) We found an upregulation of MMP-9 expression and activity in the infarcted area of the LV. The endogenous MMP inhibitor TIMP-1 was also increased in the current study after MI, but, interestingly, this was even more pronounced after aliskiren treatment, which may be associated with changes in the activation of the MAP kinases. This endogenous inhibition of MMP activity might further have contributed to the observed decrease in LV dilatation after MI, because renin inhibition attenuated the activity of MMP-9, documented by a decreased MMP-9:TIMP-1 ratio and decreased MMP-9 activity in zymography. Taken together, the attenuation of MMP activity, which can be achieved by RAS inhibition, might, therefore, be an important factor in preventing post-MI LV. Moreover, because MMP-9 is associated with tissue inflammation, further studies have to focus on the influence of aliskiren on post-MI inflammation.

Some limitations of our study should be acknowledged. Animals with small infarct sizes were excluded from this study to rule out any influence of infarct size on hemodynamic function. Therefore, future studies have to evaluate whether treatment with aliskiren might have an impact on the infarct size. We showed that the chosen dose of aliskiren was not blood pressure lowering after 10 days, which is in line with findings of others,\(^7\) but it has to be remembered that small reductions of blood pressure during the time course of this study might also have had an impact on the complex interplay between the development of systolic dysfunction and post-MI.

**Perspectives**

We have shown here that suppressor pharmacological inhibition of renin attenuates cardiac dysfunction after MI in mice. These changes are associated with decreased post-MI hypertrophy, apoptosis, and changes in the MMP activity. This effect was independent of blood pressure lowering; therefore, it is intriguing to speculate that renin inhibition can prevent cardiac remodeling after MI also in patients and that this effect will not only depend on blood pressure lowering. Nevertheless, clinical trials will have to evaluate this effect and have to prove that renin inhibition might be suitable for treating heart failure in humans.

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**Disclosures**

None.

**References**


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