Effect of a selective aldosterone receptor antagonist in myocardial infarction

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Delyani, John A., Eric L. Robinson, and Amy E. Rudolph. Effect of a selective aldosterone receptor antagonist in myocardial infarction. Am J Physiol Heart Circ Physiol 50: H647–H654, 2001.—Myocardial infarction (MI) initiates adaptive tissue remodeling, which is essential for heart function (such as infarct healing) but is also important for maladaptive remodeling (for example, reactive fibrosis and left ventricular dilation). The effect of aldosterone receptor antagonism on these processes was evaluated in Sprague-Dawley rats using eplerenone, a selective aldosterone receptor antagonist. Infarct healing and left ventricular remodeling were evaluated at 3, 7, and 28 days after MI by determination of the diastolic pressure-volume relationship of the left ventricle, the infarct-thinning ratio, and the collagen-volume fraction. Eplerenone did not affect reparative collagen deposition as was evidenced by a similar collagen volume fraction in the infarcted myocardium between eplerenone and vehicle-treated groups at 7 and 28 days post-MI. In addition, the thinning ratio, which is an index of infarct expansion, was comparable between the eplerenone and vehicle-treated animals at 7 and 28 days post-MI. A protective effect of eplerenone was demonstrated at 28 days post-MI, where reactive fibrosis in the viable myocardium was reduced in eplerenone-treated animals compared with vehicle-treated animals. Thus aldosterone receptor antagonism does not retard infarct healing but rather protects against maladaptive responses after MI.

LV function and survival rates after MI. Examples include agents that act by inhibiting the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme (ACE) inhibitors (22) and AT1-receptor antagonists (8), both of which have been shown to reduce LV dilation and fibrosis in the remote myocardium without affecting scar formation and stabilization. In contrast, glucocorticoids (20), ibuprofen (5, 6), and more recently endothelin receptor antagonists (21) have been shown to exacerbate infarct expansion and retard reparative collagen deposition in the infarcted myocardium; these events can lead to worsening of LV dysfunction, ventricular aneurysm, and, in extreme cases, ventricular rupture.

Several groups have demonstrated that aldosterone receptor antagonism can attenuate aldosterone-mediated reactive cardiac fibrosis (2, 3, 12, 13, 27, 30). Although it is well accepted that aldosterone can stimulate reactive fibrosis, the role of aldosterone in reparative myocardial fibrosis is unknown. Using the selective aldosterone antagonist eplerenone (Epl), we evaluated the contribution of aldosterone to acute infarct expansion and late-phase remodeling in a well-characterized model of MI.

METHODS

Surgical model of MI. All studies were conducted using an approved protocol from the Monsanto/Searle Institution for Animal Care and Use Committee and are in accordance with the guidelines set by the Association for the Assessment and Accreditation of Lab Animal Care for the use of experimental animals. Male Sprague-Dawley rats (220–250 g body wt) were utilized for this study. Animals were anesthetized with 5% isoflurane and were intubated and ventilated at 52 respirations/min (3 ml/respiration) while anesthesia was maintained using 2–3% isoflurane. A left thoracotomy was performed and the heart was exposed. Silk suture (4.0) was placed around the left coronary artery ~5 mm from its origin, and the artery was either ligated (in MI animals) or left untied (in sham-MI animals). The thorax was closed with layered sutures. Animals were monitored on a heating pad during recovery from anesthesia and for 12 h thereafter.

Twenty-four hours after surgery, 76 animals were randomly assigned to be treated with oral administration (150 mg/kg twice daily) of either methyl cellulose vehicle (Veh) or eplerenone.

Changes to left ventricular (LV) geometry and tissue constituent after myocardial infarction (MI) can be arbitrarily divided into acute and chronic phases. The acute phase (termed “infarct expansion”) typically occurs in the first days after MI and is defined by thinning of the infarcted myocardium and dilation of the ventricular cavity (9, 24). The second phase, which begins after stabilization of the infarct scar and may continue indefinitely, is characterized by continued ventricular dilation as well as hypertrophy and reactive fibrosis of the remote noninfarcted myocardium (29). Infarct expansion, late-phase ventricular dilation, and fibrosis of viable myocardium are all maladaptive processes that contribute to LV dysfunction and the progression to heart failure.

Agents that reduce one or more of these processes without affecting the healing of the infarction improve LV function and survival rates after MI.
Epl for 3, 7, or 28 days. There were no differences in mortality between groups entered into this study before the 28-day time point. To account for any increases in body weight, the animals were weighed every 7 days, and solution concentrations (milligrams per milliliter) were adjusted accordingly. At cessation of the experiments (i.e., 3, 7, or 28 days post-MI surgery), the animals were anesthetized with pentobarbital sodium (65 mg/kg ip), and body weights were determined.

Assessment of LV compliance and histology. The heart was arrested in diastole by injection of a saturated potassium chloride solution. The thorax was opened and the heart was rapidly removed. Excess tissue and vasculature was trimmed and heart weight was obtained. The LV pressure-volume relationship was determined using methods previously described (10). In brief, a double-lumen cannula [polyethylene (PE)-50 tubing inside PE-200 tubing] was inserted into the left ventricle via the aortic valve. An incision was made in the right ventricular (RV) free wall (FW) to prevent any compressive force that might have been applied to the interventricular septum by the RV wall while the left ventricle was being expanded with fluid. The interventricular groove was isolated using 3.0 silk suture to isolate the left atrium from the left ventricle, and fluid was expelled from the ventricle to create a pressure of ~0 mmHg. Sodium chloride solution (0.9%) was infused at 0.68 ml/min via one lumen using a syringe pump while intraventricular pressure was simultaneously recorded through the other lumen using a fluid-filled pressure transducer connected to a heart-performance analyzer/recorder (Micro-Med; Louisville, KY). Pressure was recorded over the range of 0–40.0 mmHg and the infusion was stopped. A minimum of two and a maximum of three pressure-volume curves were obtained within 10 min after cardiac arrest. LV volumes at pressures of 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 40 mmHg were then determined using Digi-Med System Integrator 200/1 software.

After pressure-volume measurements were made, hearts were gravity perfusion fixed at 100 mmHg with 10% neutral-buffered formalin and were subsequently immersed in 10% neutral buffered formalin for 7 days. The major veins and atria were then removed from the ventricles, and the right ventricle was carefully separated from the left ventricle. The left ventricles were placed in a rat heart matrix and cut into five cross-sectional samples of ~2 mm each. The five regions were then processed into paraffin with an automated tissue processor. After processing was completed, the samples were embedded into fresh paraffin with the apical side down. Those samples were then cut into 10-μm sections and were mounted on slides; 5-μm sections were also cut from each block adjacent to the 10-μm section and were mounted in the same fashion. The 5-μm sections were used for hematoxylin and eosin staining, and the 10-μm sections were stained with the collagen-specific stain picrosirius red F3BA. The 10-μm mounted tissues were hydrated with water and placed in xylene baths. Tissues were then incubated twice in 100% ethanol (for 1 min each) and cleared twice in xylene baths. After incubation for 20 min at 4°C with intermittent shaking, tissues were centrifuged at 1,000 g for 5 min, the supernatant was aspirated, and the pellet was washed three times with 1 ml of ice-cold buffer (which contained 8.5 mM Na2HPO4, 1.5 mM KH2PO4, and 2 mM monothioglycerol and 20% glycerol by volume) at pH 7.4. Homogenates were centrifuged at 150,000 g for 60 min at 4°C. Cytosolic protein levels were determined by the Bradford assay (1).

Rat-colon cytosol (100 μl) was incubated for 16–18 h at 4°C with 100 μl of a 2 nM tracer ([3H]aldosterone plus 1 nM RU-38486, a glucocorticoid and progesterone receptor antagonist; Roussel-UCLAF, Paris, France) and Epl (0, 1, 3, 10, 100, 1,000, and 10,000 nM) to yield a total incubation volume of 300 μl. The identical procedure was performed using aldosterone as a control.

Bound and free steroids were separated by the addition of 300 μl of an ice-cold suspension of hydroxyapatite (HAP; 15% wt/vol) in 50 mM Tris-HCl and 10 mM KH2PO4 at pH 7.2. After incubation for 20 min at 4°C with intermittent shaking, samples were centrifuged at 1,000 g for 5 min, the supernatant was aspirated, and the pellet was washed three times with 1 ml of ice-cold buffer (which contained 8.5 mM Na2HPO4, 1.5 mM KH2PO4, and 10 mM NaMo4 at pH 7.2). Washed HAP pellets were resuspended in 2 ml of ethanol at room temperature for 15 min and centrifuged at 1,000 g for 5 min before the supernatant was counted.
Test compound. Veh was 0.5 mg/ml methyl cellulose solubilized in deionized water. Epl was suspended in the 0.5 mg/ml methyl cellulose solution. Veh solutions and test compounds were administered in identical volumes. Epl and Veh were orally administered twice daily in doses of 150 mg/kg. This dose has previously been determined to exceed the maximal efficacious dose and yet not precipitate any adverse effects in the rat; thus the lack of effect on healing cannot be attributed to the use of a submaximal dose.

Statistical analysis. Seven parameters were analyzed at 3, 7, and 28 days postsurgery: body weight, heart weight-to-body weight ratio, infarct-thinning ratio, infarct and noninfarct collagen-volume fraction, infarct size, and LV diastolic pressure-volume relationship. Data are expressed as means ± SE. Groups were compared using one-way ANOVA and post hoc analysis of either Tukey-Kramer honestly significant difference (to compare between treatment groups) or Dunnett’s test (to compare treatment groups to control) using statistical software (JMP 3.0 for Macintosh; SAS Institute; Cary, NC). P ≤ 0.05 was used to demonstrate statistical significance.

RESULTS

Steroid receptor binding of Epl. The IC\textsubscript{50} of Epl for the mineralocorticoid receptor was 360 nM, whereas the IC\textsubscript{50} values calculated for the androgen, progesterone, and estrogen receptors were all >10,000 nM. Thus Epl is at least 27 times as selective for the mineralocorticoid receptor. These data are consistent with those reported elsewhere in which Epl was shown to be ~100- and 1,000-fold sparing for the progesterone and androgen receptors, respectively (7).

Day 3 post-MI. There were no significant changes in body or heart weight between any of the experimental groups (see Table 1) 3 days after MI. Because the size of the MI plays an important role in the extent of infarct expansion (23), this parameter was also determined and is shown in Table 1. The percentage of the left ventricle that was rendered necrotic was compared and is shown in Table 1. The percentage of the left ventricle that was rendered necrotic was compared and is shown in Table 1. The percentage of the left ventricle that was rendered necrotic was similar to that of the MI-Veh group (4.6 ± 0.6 vs. 5.2 ± 0.8). Figure 1B shows the extent of collagen deposition in the viable myocardium. Although there is a trend for increased collagen deposition in the groups suffering infarction compared with the sham-operated control, these values did not reach statistical significance. The thinning ratio at day 3 is shown in Fig. 1C. As expected, sham-MI animals had a ratio of nearly 1 (0.96 ± 0.05; range 1.19–0.80). The MI-Veh group had a mean similar to the sham-MI group. However, the variability was more pronounced (0.93 ± 0.08; range 1.2–0.5), and some values were markedly <1, which indicates thinning of affected myocardium in some of the animals. The MI-Epl group also had animals with evidence of infarct thinning at this early time point. However, in the Epl-treated animals, the thinning ratio (0.71 ± 0.06) was statistically less than in the sham-MI group and had values with a similar range of those of the MI-Veh group (range 1.1–0.5). The passive diastolic pressure-volume relationship of animals at day 3 is

<table>
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<tr>
<th>Group</th>
<th>BW, kg</th>
<th>HW, g</th>
<th>HW/BW, g/kg</th>
<th>Infarct Size, %LV</th>
</tr>
</thead>
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<tr>
<td>MI-sham</td>
<td>0.26 ± 0.01</td>
<td>0.98 ± 0.02</td>
<td>3.74 ± 0.11</td>
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<tr>
<td>MI-Veh</td>
<td>0.25 ± 0.01</td>
<td>1.14 ± 0.05</td>
<td>4.54 ± 0.38</td>
<td>42.28 ± 3.36</td>
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<tr>
<td>MI-Epl</td>
<td>0.26 ± 0.01</td>
<td>1.09 ± 0.02</td>
<td>4.14 ± 0.18</td>
<td>47.57 ± 1.82</td>
</tr>
</tbody>
</table>

Values are means ± SE. Epl, eplerenone; Veh, vehicle; LV, left ventricle; MI, myocardial infarction; BW, body weight; HW, heart weight; NA, not available.
shown in Fig. 2. At day 3 after MI, there was a comparable shift of the relationship to the left in both groups suffering MI. These results are shown histologically in Fig. 7 and are consistent with a decrease in LV compliance that has been demonstrated previously (26).

Day 7 post-MI. Body weight was similar among all groups 7 days after MI (see Table 2). An early trend of LV hypertrophy was detected in the infarcted groups, but these values did not reach statistical significance. As in the day 3 post-MI groups, infarct size was similar between the MI-Veh group and the MI-Epl group (44.1 ± 4.1 vs. 40.1 ± 6.0%) at day 7. The collagen-volume fraction in the infarcted area of the MI-Veh group is shown in Fig. 3A. The collagen deposition in the infarcted area increased 10-fold (5–50%) from day 3 to day 7, which indicates rapid and extensive replacement of necrotic tissue with collagen during this time period. As described for day 3, the extent of replacement fibrosis was similar in the infarcted area of the MI-Epl group to that of the MI-Veh group, which indicates that Epl did not reduce collagen deposition up to 7 days post-MI. Reactive fibrosis, as indexed by the collagen-volume fraction in the viable myocardium (see Fig. 3B), was not statistically significant at day 7. Infarct expansion was present in both MI groups at day 7 as is reflected by both the thinning ratio and the pressure-volume relationship. LV wall thinning at day 7 was also evident histologically in Fig. 7. The thinning ratio of both MI groups was similar and markedly less (by ∼50%) than that of the sham-MI group (see Fig. 3C and Table 2). The pressure-volume relationship at day 7 is shown in Fig. 4. The marked rightward shift in both MI groups is likely to be primarily due to increased wall thinning in these groups and changes in wall compliance. Therefore, ventricular remodeling was evidenced at day 7 after MI, and the extent of remodeling was similar in both MI groups at this early time point.

Day 28 post-MI. The body weights of the MI-Veh and MI-Epl groups were 94 and 92% of the sham-MI group, respectively, with the MI-Epl group being statistically less than the sham-MI group (Table 3). Both MI groups exhibited myocardial hypertrophy as indexed by the heart weight-to-body weight ratio, which is consistent with known post-MI tissue remodeling. The percentage of the left ventricle that was infarcted was similar in the MI-Veh and MI-Epl groups (36.0 ± 1.6 vs. 37.7 ± 2.9%); thus any differences in ventricular remodeling or tissue constituency are unlikely to be explained by

![Fig. 2. Effect of Veh and Epl treatments on ex vivo passive diastolic pressure-volume relationship 3 days post-MI. LV volume was measured during saline infusion over the pressure range of 0–40 mmHg after diastolic arrest. ■, 3-day sham (n = 7); ▲, 3-day MI (n = 7); ●, 3-day MI-Epl (n = 9). Values are means ± SE.](http://ajpheart.physiology.org/)

![Fig. 3. Effect of Epl on cardiac and reparative fibrosis 7 days after MI. Myocardial tissues were stained for collagen with picrosirus red, and CVF of infarcted (A) and viable (B) myocardium was determined based on percent collagen in five cross-sectional samples of each heart. Thinning ratio of LV free wall (C) was determined after hematoxylin and eosin staining. Values are means ± SE. *P < 0.05 compared with sham.](http://ajpheart.physiology.org/)
differing degrees of myocardial injury. At 28 days post-MI, the infarct collagen deposition in the MI-Veh group increased further from day 7 (from 47.1 ± 4.4 to 59.5 ± 2.5%; see Fig. 5A). Similar to earlier time points, the MI-Epl group had a comparable fraction of collagen in the infarcted region compared with the MI-Veh group, thereby demonstrating that selective aldosterone receptor antagonism did not reduce scar-collagen deposition at this late time point.

Unlike the collagen-volume fraction in the infarcted region, there was a difference among experimental groups in the viable myocardium. The viable myocardium of the MI-Veh group but not the MI-Epl group had a significantly greater collagen-volume fraction than the sham-MI group (see Fig. 5B). These data demonstrate that reactive fibrosis occurred in the viable myocardium after infarction, and that Epl attenuated this process in a significant fashion compared with the MI-Veh group (see Fig. 5B). As anticipated, there was substantial infarct thinning in both MI groups. The thinning ratios of the MI-Epl and MI-Veh groups were similar and were ~40% of the sham-MI group (see Fig. 5C). The pressure-volume relationship (an index of ventricular remodeling) of the MI-Veh group but not the MI-Epl group was significantly shifted to the right compared with the sham-MI group (see Fig. 6). Additionally, LV wall thinning as well as ventricular dilation were detected histologically at 28 days (see Fig. 7).

**DISCUSSION**

Brilla and co-workers (2, 3) first demonstrated that aldosterone could mediate reactive interstitial myocardial and coronary vascular fibrosis. These data were later confirmed and extended by Young and colleagues.

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**Table 3. Effect of Epl treatment on hypertrophy and fibrosis 28 days post-MI**

<table>
<thead>
<tr>
<th>Group</th>
<th>BW, kg</th>
<th>HW, g</th>
<th>HW/BW, g/kg</th>
<th>Infarct Size, %LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI-sham</td>
<td>0.36 ± 0.01</td>
<td>1.22 ± 0.04</td>
<td>3.34 ± 0.08</td>
<td>NA</td>
</tr>
<tr>
<td>MI-Veh</td>
<td>0.34 ± 0.01</td>
<td>1.29 ± 0.03</td>
<td>3.73 ± 0.12</td>
<td>36.00 ± 1.56</td>
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<tr>
<td>MI-Epl</td>
<td>0.39 ± 0.01*</td>
<td>1.29 ± 0.03</td>
<td>3.85 ± 0.08*</td>
<td>37.72 ± 2.89</td>
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</tbody>
</table>

*Values are means ± SE. *P < 0.05, significantly different from MI-sham control values.
Aldosterone Antagonism and Myocardial Infarction

The thinning ratio at day 3 was less in the MI-Epl-treated group than the MI-Veh-treated group. Although it cannot be definitively demonstrated that Epl did not potentiate scar thinning at this early time point, it is unlikely for the following reasons. First, the collagen volume fraction of the two MI groups at day 3 were similar. Second, scar thinning at the late inflammatory stage (day 7) and the stable infarct stage (day 28) was similar among the two MI groups, and the pressure-volume relationship at any time point did not support a role for Epl in increasing infarct expansion. Thus a more probable hypothesis is that the observation reflects alterations in the transition of the acute necrotic myocardium from an edematous state to reparative replacement of the necrotic tissue and subsequent scar thinning. This hypothesis is supported by data showing that in early stages after coronary artery occlusion the affected myocardium became swelled and edematous (which was reflected by a thinning ratio of >1). Only at later time points did the affected myocardium thin as the necrotic tissue was replaced by collagen (15).

As noted, the scar thinning and the pressure-volume relationships at days 7 and 28 were similar among the two MI groups. These data are in contrast to other studies in which anti-inflammatory therapies have demonstrated interruption of the myocardial infarct healing process (5, 6, 17) and, most recently, potentiation of infarct expansion by an endothelin receptor antagonist in the same animal model (21). Our data do, however, support the hypothesis that blocking the actions of aldosterone after MI is safe and will not result in disruption of the myocardial infarct healing process.

Agents that interrupt the RAAS have been shown to attenuate LV remodeling. These effects were first demonstrated by the ACE inhibitor captopril (22–25); this result was later shown to be a pharmacological class effect (19, 28). Protective agents were later extended to include AT1-receptor antagonists (8) as well as other pharmacological therapies with a non-RAAS mechanism of action (16).

Our data extends the concept of blocking the RAAS in an attempt to prevent remodeling to antagonizing the actions of aldosterone. This extension is supported by our data showing that the pressure-volume relationship of the Veh-treated but not the Epl-treated animals suffering MI was significantly shifted to the right of the relationship of sham-operated control animals (see Fig. 6). However, it should be noted that the heart weight-to-body weight ratio, which is an index of hypertrophy, was similar between groups. Although it is unclear why Epl did not reduce this index as many other RAAS acting agents have been shown to do, this finding may be due to the nonvasodilatory mechanism of Epl which is distinct from ACE inhibitors and AT1-receptor antagonists.

The present study demonstrates that selective aldosterone receptor antagonist reduces reactive but not reparative fibrosis. It is likely that the mediators of reactive and reparative fibrosis are different. Although the mechanism of aldosterone action in reactive fibro-

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Fig. 7. Midcoronal cross sections of LV at 3, 7, and 28 days post-MI displaying LV dilation and wall thinning with Veh and Epl treatments.

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Table:

<table>
<thead>
<tr>
<th>3 Days</th>
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<th>28 DAYS</th>
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<tbody>
<tr>
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<td>MI + Vehicle</td>
<td>MI + Vehicle</td>
</tr>
<tr>
<td>MI + Eplerenone</td>
<td>MI + Eplerenone</td>
<td>MI + Eplerenone</td>
</tr>
<tr>
<td>Sham + Veh</td>
<td>MI + Vehicle</td>
<td>MI + Vehicle</td>
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</table>

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30) and others (12, 13, 27). From these established observations, we hypothesized that aldosterone may also be an important player in the development of myocardial reparative fibrosis and myocardial infarct healing. The role of aldosterone in these processes was assessed using the selective aldosterone receptor antagonist Epl. Epl receptor binding activity was assessed in this study and found to be consistent with results from other investigators; namely, the affinity of Epl for the mineralocorticoid receptor is much higher than the affinity for other steroid receptors, which justifies its classification as a selective aldosterone receptor antagonist. This pharmacological characteristic of Epl contrasts with spironolactone, the other clinically relevant aldosterone receptor antagonist. Spironolactone is known to be an effective antagonist of the mineralocorticoid receptor. However, it also potently inhibits the androgen and progesterone receptors, which results in steroid-related side effects that limit its therapeutic utility and confound the interpretation of experimental results.

The results from this study demonstrate that selective aldosterone receptor antagonism by Epl after MI does not have detrimental effects on tissue remodeling. Specifically, Epl did not exacerbate infarct expansion as indexed by the pressure-volume relationship or the infarct-thinning ratio, nor did it slow reparative fibrosis as indexed by collagen deposition in the myocardial scar. In fact, these data demonstrate that Epl has a protective effect on maladaptive post-MI processes, as evidenced by attenuated reactive fibrosis in noninfarcted viable myocardium and reduced LV remodeling.
sis is incompletely understood, it has been proposed (4) that excess collagen production by stimulated cardiac fibroblasts may be a contributing factor. The mediators of collagen production in myocardial reparative fibrosis have yet to be fully elucidated. However, the redundant nature of the process, i.e., increased collagen production stimulated by other factors such as ANG II, endothelin, and transforming growth factor-β may allow for sufficient stimulation and appropriate collagen deposition. In fact, ACE inhibitors (22) and AT₁ receptor antagonists (8) have also been shown not to impair the infarct healing response after MI.

At 28 days postinfarction, the pressure-volume relationship for MI-Veh animals was significantly shifted compared with sham-MI animals, whereas the MI-Epl group was not significantly different from the sham-MI group. These data support a role for aldosterone in ventricular remodeling after infarction. Future studies directly addressing this hypothesis and its underlying mechanisms are warranted. These data are unlikely to be the result of a diuretic effect, because other much more potent diuretics fail to demonstrate protective effects in this model on characteristics of remodeling (14, 18). In addition, a role for aldosterone in fibrosis and remodeling is especially significant given that the rat MI model is not characterized by chronic activation of RAAS, which suggests that normal plasma aldosterone levels are sufficient to support a role in post-MI remodeling. This finding is novel and in contrast to the previously mentioned studies, which implicate aldosterone in cardiac fibrosis by the use of animal models characterized by markedly elevated plasma aldosterone levels and high-salt diets. One explanation that may unify these current results with previous studies lies in recent findings that describe the activation of local aldosterone production in the heart after MI (27). In the microenvironment of the myocardium, the aldosterone concentration may be significantly higher than in plasma levels, which could potentially contribute to tissue remodeling and fibrosis after MI.

In summary, these data demonstrate that selective aldosterone receptor antagonism does not adversely affect myocardial infarct healing. The study supports the hypothesis that normoaldosteronemia is sufficient to mediate maladaptive myocardial remodeling and that a selective aldosterone receptor antagonist can attenuate these effects. The mechanism by which aldosterone plays a role in post-MI remodeling is currently being investigated.

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REFERENCES


