Immediate Administration of Mineralocorticoid Receptor Antagonist Spironolactone Prevents Post-Infarct Left Ventricular Remodeling Associated With Suppression of a Marker of Myocardial Collagen Synthesis in Patients With First Anterior Acute Myocardial Infarction

Masaru Hayashi, MD; Takayoshi Tsutamoto, MD; Atsuyuki Wada, MD; Takashi Tsutsui, MD; Chitose Ishii, MD; Keijin Ohno, MD; Masanori Fujii, MD; Atsushi Taniguchi, MD; Tomokazu Hamatani, MD; Yoshitaka Nozato, MD; Ken Kataoka, MD; Naoki Morigami, MD; Masato Ohnishi, MD; Masahiko Kinoshita, MD; Minoru Horie, MD

Background—Aldosterone (ALD) has been shown to stimulate cardiac collagen synthesis and fibroblast proliferation via activation of local mineralocorticoid receptors. In patients with acute myocardial infarction, we demonstrated that ALD was extracted through the infarct heart and extracting ALD-stimulated post-infarct left ventricular (LV) remodeling.

Methods and Results—To evaluate the effect of mineralocorticoid receptor antagonist (MRA) spironolactone on post-infarct LV remodeling, 134 patients with first anterior acute myocardial infarction were randomly divided into the MRA (n=65) or non-MRA (n=69) groups after revascularization. All patients were administered angiotensin-converting enzyme (ACE) inhibitor and study drug just after revascularization. Left ventriculography with contrast medium was performed at the acute stage and after 1 month to evaluate LV remodeling. ALD was measured at aortic root and coronary sinus. There was no difference in the baseline characteristics including infarct size and LV performance between the two groups. However, LV ejection fraction was significantly improved in the MRA group compared with that in the non-MRA group (46.0±0.6% to 53.2±0.8% versus 46.5±0.8% to 51.0±0.8%, Pinteraction=0.012). LV end-diastolic volume index was significantly suppressed in the MRA group compared with that in the non-MRA group (86.5±1.0 to 90.6±2.4 versus 87.5±1.3 to 106.8±3.5 mL/m², Pinteraction=0.002). Transcardiac extraction of ALD through the heart was significantly suppressed in the MRA group (Pinteraction=0.001), and plasma procollagen type III aminoterminal peptide level, a biochemical marker of fibrosis, was significant lower in the MRA group compared with the non-MRA group (Pinteraction=0.002).

Conclusions—These findings indicate that MRA combined with ACE inhibitor can prevent post-infarct LV remodeling better than ACE inhibitor alone in association with the suppression of a marker of collagen synthesis. (Circulation. 2003;107:2559-2565.)

Key Words: myocardial infarction ▪ ventricles ▪ remodeling ▪ collagen

Aldosterone (ALD) displays both myocardial and renal effects that may have profound implications for left ventricular (LV) remodeling.1 In the Randomized Aldactone Evaluation Study (RALES), mineralocorticoid receptor antagonist (MRA) spironolactone was shown to reduce mortality in patients with congestive heart failure (CHF),2 and the beneficial outcome in RALES was shown to be associated with the suppression of the marker of cardiac collagen synthesis by spironolactone.3 Moreover, ALD levels have been found to increase in some patients with acute myocardial infarction (AMI), with profound implications for LV remodeling and long-term prognosis.4,5 We demonstrated that one of the mechanisms involved preventing post-infarct LV remodeling was the suppression of plasma ALD during the acute phase of AMI.6 These results suggested that endogenous ALD and mineralocorticoid receptor may play an important role in the progression of post-infarct LV remodeling.

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Recently, it has been shown that mineralocorticoid receptor, which mediates the action of ALD, is expressed in human
heart, suggesting that the heart is a target organ of ALD. We reported that plasma ALD was extracted through the heart in patients with chronic CHF and that the transcardiac gradient of plasma ALD was correlated with LV end-diastolic volume index (LVEDVI) and plasma levels of procollagen type III aminoterminal peptide (PIIINP), a marker of myocardial fibrosis. Moreover, we recently demonstrated that in patients with AMI, plasma ALD was extracted through the heart from acute to subacute stage, and transcardiac extraction of ALD at the acute stage, associated with cardiac fibrosis, positively correlated LVEDVI 1 month after onset, suggesting ALD extraction into the infarcted heart stimulates post-infarct LV remodeling. However, the effects of blocking the mineralocorticoid receptors immediately after AMI onset if extraction of ALD is suppressed by MRA, was administrated. Starting on day 1, oral spironolactone (25 mg/d) was administrated in the MRA group. ACE inhibitors (Enalapril) were started 1 day after onset at 2.5 mg daily to all patients. If required, oral nitrates, calcium antagonists, β-blockers, or diuretics were added and continued. Aspirin was administrated to all patients. Patients with worsening renal failure (creatinine >2.0 mg/dL) or hyperkalemia (serum potassium >5.5 mEq/dL) were excluded from the study.

Repeat cardiac catheterization and contrast left ventriculography were performed 1 month after onset. Contrast left ventriculography was performed to analyze LV ejection fraction (LVEF) and LV volume by cardiologists who were unaware of the patients’ data. LVEF was calculated by the area-length method. Hemodynamic measurement and blood sampling were also performed. Patients with significant restenosis (>70%) of the culprit lesion were excluded from the study.

Measurement of Neurohumoral Factors
Plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were measured with a specific immunoradiometric assay using a commercial kit (Shionogi) as previously reported. Plasma ALD levels were measured using a commercial radioimmunoassay kit, and plasma levels of PIIINP were measured with a specific immunoradiometric assay using a commercial kit (CIS Bio International) as previously reported.

Statistical Analysis
All results are expressed as mean ± SEM. Univariate analyses were performed using Student’s t test for continuous variables. Categoric data were compared against a χ² distribution. Responses after MRA therapy were compared with those without MRA therapy using 2-way ANOVA. When significant differences were observed, comparison within groups or drug treatments were performed with ANOVA by Schéffe’s F test or paired Student’s t test. Comparison between the two groups at each time point was performed using unpaired t test. Comparison within the groups at each point was performed using paired t test. To evaluate the contribution of LV remodeling 1 month after onset, univariate and stepwise multivariate analyses were used among the 14 variables. P < 0.05 was regarded as significant.

Results
Clinical Characteristics
One hundred fifty consecutive patients who met entry criteria were enrolled. Seventy-five patients were randomized to the MRA treatment group, and 75 to the group without MRA. In the MRA group, 2 patients died due to lethal arrhythmia and 2 due to CHF, and 2 were excluded because of restenosis in the culprit lesion, 2 because of gynecomastia, and 2 because of worsening renal function. In the non-MRA group, 2 patients died due to CHF, 1 due to lethal arrhythmia; 3 were excluded because of restenosis. Therefore, 134 of 150 patients enrolled in the trial completed the entire protocol. There was no difference in baseline characteristics, including infarct size, LV volume, and function value. There was also no difference in acute to subacute therapy, including the doses of ACE inhibitor enalapril between the two groups. The dose of β-blockade (carvedilol) in this study was 5.8 mg daily, which is similar in both groups. Baseline characteristics are listed in Table 1.

LV Volume and Function
There was no difference in LVEF at baseline, and it was significantly increased after 1 month in both groups (MRA, P < 0.0001; non-MRA, P < 0.0001 within each group), but the improvement in LVEF with MRA was significantly greater than that without MRA. The absolute change in LVEF in the
MRA group was significantly higher than that of the non-MRA group (7.20 ± 0.7% vs 4.46 ± 0.8%, P < 0.05), and LVEF at 1 month in the MRA group was significantly higher than that in the non-MRA group. There was no difference in LVEDVI at baseline. LVEDVI was significantly increased after 1 month in both groups (MRA, P < 0.05; non-MRA, P < 0.0001 within each group). However, in the MRA group, the absolute change in LVEDVI was significantly suppressed (4.0 ± 2.1 vs 19.2 ± 3.2 mL/m², P < 0.001) compared with that in non-MRA group. In MRA group but not in non-MRA, an increase in LVEDVI was prevented. There was no difference of LVESVI at baseline, and the LVESVI significantly increased in the non-MRA group (P < 0.01 from baseline within non-MRA group) but was significantly decreased in the MRA group (P < 0.01 from baseline within MRA group) (Figure 1, Table 2).

Neurohumoral Factors and Plasma PIIINP

At baseline, there was no significant difference in plasma levels of ALD in Ao between the two groups. One month after onset, the plasma ALD in Ao was significantly suppressed in both groups. However, ALD in Ao was significantly higher in the MRA group compared with that in the non-MRA group (Table 2).

Transcardiac extraction of ALD through the heart at baseline was similar in both groups. After 1 month, transcardiac extraction of ALD was significantly decreased in both groups. However, suppression of transcardiac extraction of ALD in the MRA group was greater than that in non-MRA group. The transcardiac extraction of ALD was significantly suppressed in the MRA group compared with that in the non-MRA group (6.7 ± 1.9 vs 18.4 ± 2.1 pg/mL, P < 0.0001). The transcardiac extraction of ALD through the heart at the acute stage was positively correlated with that 1 month after onset in both MRA group (r = 0.599, P < 0.0001)

![Figure 1. Top, Changes in the LVEF, LVEDVI, LVESVI in the two randomized treatment groups from baseline to 1 month later. Bottom, Absolute change (value at 1 month - baseline) in LVEF, LVEDVI, and LVESVI. †P < 0.05; ‡P < 0.01; §P < 0.0001: difference between baseline and 1-month values (within each group).](http://circ.ahajournals.org/)}
and non-MRA group ($r=0.643$, $P<0.0001$), as shown in Figure 2.

There was no significant difference in baseline PIIINP between the two groups, and PIIINP was significantly increased after 1 month in both groups (MRA, $P<0.001$; non-MRA, $P<0.0001$ within each group). However, the elevation of PIIINP in MRA group was significantly suppressed compared with that in non-MRA. Furthermore, absolute change of PIIINP was significantly lower in MRA group than in non-MRA. As shown in Figure 3, absolute change in LVEDVI was positively correlated with the absolute change in PIIINP.

**Hemodynamic Parameters**

There was no difference in hemodynamic parameters at baseline between the two groups. Moreover, there were no significant differences in serial changes in these hemodynamic parameters between the two groups. Serial increases in serum creatinine level were similar in both groups; however, serum potassium level was significantly increased in the MRA group compared with the non-MRA group (Table 3).

**Evaluation of Factors Regulating LV Remodeling**

Table 4 shows the results of univariate and multivariate analysis among 14 variables related to the acute phase to assess factors regulating the absolute change in LVEDVI from acute to 1 month after onset. According to stepwise multivariate analysis, only no administration of MRA ($P<0.0001$), a high level of transcardiac extraction of ALD at the acute phase ($P<0.0001$), a high level of maximum creatine phosphokinase ($P=0.0004$), and poor performance of LVEF at the acute phase ($P=0.0236$) were significant independent predictors of an enlargement of LVEDVI during 1 month after onset.

**Discussion**

Our findings in this study demonstrate for the first time that combination therapy with a MRA and ACE inhibitor started at onset immediately after revascularization can prevent LV dilatation more effectively and improve the LVEF in patients with a first anterior AMI better than ACE inhibitor alone, that MRA suppresses transcardiac extraction of ALD through the heart during acute to subacute phase of AMI, and that MRA suppressed cardiac collagen synthesis occurring during acute to subacute phase of AMI. These results indicate that treatment with MRA combined with ACE inhibitor prevents post-infarct LV remodeling associating with suppression of a marker of collagen synthesis compared with that achieved by ACE inhibitor alone in patients with AMI.

**Dose Setting of MRA**

We chose an MRA starting dose of 200 mg of canrenoate in bolus injection, because in our preliminary study, reduction of the preload, urination, and blood pressure had a less acute effect.

![Figure 2](http://circ.ahajournals.org/)

**Table 2.** Changes in LV Performance and Neurohumoral Factors From Baseline to 1 Month

<table>
<thead>
<tr>
<th></th>
<th>MRA (n=65)</th>
<th>Non-MRA (n=69)</th>
<th>$P$, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Month</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>LV performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>$46.0 \pm 0.6$</td>
<td>$53.2 \pm 0.8^*$</td>
<td>$46.5 \pm 0.8$</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>$86.5 \pm 1.0$</td>
<td>$90.6 \pm 2.4^†$</td>
<td>$87.5 \pm 1.3$</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>$47.3 \pm 1.0$</td>
<td>$43.4 \pm 1.7^‡$</td>
<td>$46.6 \pm 1.2$</td>
</tr>
<tr>
<td><strong>Neurohumoral factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD in Ao, pg/mL</td>
<td>$121 \pm 6.4$</td>
<td>$92.0 \pm 6.0^*$</td>
<td>$119 \pm 7.7$</td>
</tr>
<tr>
<td>(Ao-CS) ALD, pg/mL</td>
<td>$22.9 \pm 2.7$</td>
<td>$5.43 \pm 1.46^*$</td>
<td>$23.1 \pm 2.5$</td>
</tr>
<tr>
<td>PIIINP in CS, pg/mL</td>
<td>$0.39 \pm 0.01$</td>
<td>$0.43 \pm 0.01^§$</td>
<td>$0.38 \pm 0.01$</td>
</tr>
</tbody>
</table>

$^*P<0.0001$, $^†P<0.05$, $^‡P<0.01$, $^§P<0.001$: difference between baseline and 1-month values (within each group).
Oral MRA, spironolactone, was administered 1 day after onset at the dose of 25 mg daily, because in our previous study we found that this dose significantly diminished LV mass index in patient with CHF. In our prior study, there were no significant effects on hemodynamics and worsening renal function; therefore, we chose the MRA doses described above. Oral ACEI enalapril was started at the dose of 2.5 mg daily because, in our preliminary study, this starting dose of enalapril combined with spironolactone 25 mg daily did not excessively decrease blood pressure or worsen renal function in patients with AMI.

MRA Effect on Transcardiac Extraction of ALD
We have shown that circulating ALD was extracted across the heart, and the extraction was closely related to LV volumes in patients with CHF⁹ and AMI.¹⁰ In this study, MRA significantly suppressed transcardiac extraction of ALD through the heart. We previously reported that 20% of the plasma ALD level was extracted between the Ao and the CS in patients with CHF⁹ and that the ALD extraction ratio through the heart was 20% at the acute phase and 1 month in patients with AMI.¹⁰ The present study showed that the

![Figure 3.](image)

Table 3. Changes in Hemodynamics and Renal Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3-Day</th>
<th>1-Month</th>
<th>Group Effect</th>
<th>Time Effect</th>
<th>Group-Time Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>76.6±1.8</td>
<td>71.7±1.3#</td>
<td>67.5±1.4§</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Non-MRA</td>
<td>75.9±1.9</td>
<td>71.3±1.4†</td>
<td>68.9±1.4§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MRA</td>
<td>85.2±1.4</td>
<td>76.8±0.7§</td>
<td>88.8±1.7§</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Non-MRA</td>
<td>84.4±1.1</td>
<td>77.5±0.5§</td>
<td>88.5±1.3#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MRA</td>
<td>2.55±0.06</td>
<td>2.38±0.04†</td>
<td>2.94±0.08§</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Non-MRA</td>
<td>2.55±0.06</td>
<td>2.41±0.05†</td>
<td>2.84±0.03§</td>
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<tr>
<td>PCWP, mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>MRA</td>
<td>15.4±0.75</td>
<td>14.2±0.5</td>
<td>9.82±0.40§</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>NS</td>
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<tr>
<td>Non-MRA</td>
<td>15.9±0.42</td>
<td>14.9±0.4</td>
<td>10.4±0.41§</td>
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<td>MPA, mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>MRA</td>
<td>21.1±0.7</td>
<td>19.3±0.4#</td>
<td>14.0±0.4§</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Non-MRA</td>
<td>20.9±0.6</td>
<td>19.6±0.4#</td>
<td>13.9±0.4§</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>0.86±0.04</td>
<td>0.89±0.04</td>
<td>0.91±0.04</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Non-MRA</td>
<td>0.84±0.04</td>
<td>0.88±0.04</td>
<td>0.87±0.04</td>
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<tr>
<td>Serum kalium, mg/dL</td>
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<tr>
<td>MRA</td>
<td>4.31±0.04</td>
<td>4.49±0.03§</td>
<td>4.54±0.02§</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>0.029</td>
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<tr>
<td>Non-MRA</td>
<td>4.30±0.04</td>
<td>4.45±0.03§</td>
<td>4.46±0.02§</td>
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</table>

CI indicates cardiac index; HR, heart rate; MBP, mean arterial blood pressure; MPA, mean pulmonary arterial pressure; and PCWP, pulmonary capillary wedge pressure.

†P<0.05, #P<0.01, §P<0.0001; difference between baseline and 3-day or 1-month values (within each group).
ALD extraction ratio through the heart was ≈20% at the acute phase and 1 month in the non-MRA group; however, in the MRA group, the ALD extraction rate after 1 month was 6%, although it was 20% at acute phase. Therefore, MRA induced a 70% inhibition of ALD extraction into the heart. Moreover, transcardiac extraction of ALD at 1 month significantly and positively correlated with that at the acute stage in both MRA and non-MRA groups, indicating that ALD extraction through the heart is sustained from the acute stage to chronic stage of AMI and the level of extracting ALD is also sustained.

MRA Effect on LV Collagen Synthesis

In this study, we found that MRA significantly suppressed post-infarct elevation of PIIINP, a biochemical marker of myocardial fibrosis. Changes in PIIINP that have been shown to be induced by AMI in humans may reflect both synthesis and degradation of collagen. Aldosterone inhibition has been shown to be reduced post-infarct collagen synthesis and progressive LV dilatation in patients with subacute MI, which is consistent with our present findings in patients with acute MI; however, the mechanism was not elucidated. Previous findings showed that ALD stimulated collagen synthesis in isolated fibroblasts. Moreover, in patients with AMI, transcardiac extraction of ALD through the heart at the acute stage and 1 month after onset correlates with LV volume after 1 month, indicating sustained ALD extraction across the heart from acute to subacute stages promotes post-infarct LV collagen synthesis and remodeling. Taken together, these findings suggest that suppression of ALD extraction across the heart by MRA reduced cardiac collagen synthesis. Furthermore, high levels of plasma PIIINP in relation to ventricular fibrosis were reported to be associated with poor LV function, remodeling, and prognosis, also supporting our data.

MRA Effect on Post-Infarct LV Remodeling

In the present study, we demonstrated significant prevention of post-infarct LV remodeling in patients treated with MRA combined with ACE inhibitor compared with patients treated with ACE inhibitor alone. Furthermore, we showed that MRA significantly suppressed transcardiac extraction of ALD and post-infarct increase in PIIINP, a biological marker of cardiac fibrosis. These findings indicate that MRA inhibited the extraction of circulating ALD across the heart and suggest that it inhibits cardiac collagen synthesis and fibrosis by blocking mineralocorticoid receptors in patients with AMI.

LV remodeling was shown to be regulated by multiple factors, including mechanical, neurohumoral, and therapeutic factors. According to stepwise multivariate analysis, administration of MRA as well as infarct size were significant independent predictors of post-infarct remodeling at 1 month. This suggests that therapy with MRA starting just after onset is associated with suppression of ALD extraction and plays a significant role in preventing post-infarct LV remodeling. Regarding therapy during the acute to subacute period, there was no difference between the two groups in therapeutic strategy. In this study, all patients received revascularization and oral ACE inhibitor administration, which have been shown to prevent LV remodeling after AMI. Serial changes in hemodynamic parameters and infarct size were similar in both groups. These findings suggest suppression of post-infarct LV remodeling may be conveyed by MRA administration.

Study Limitation

This study was designed to evaluate the effect of spironolactone on post-infarct LV remodeling after 1 month. In this study protocol, all patients were administered an ACE inhibitor whose mean dose was 8.8 mg/d, if tolerated. Other
medications were not restricted. In this study, 31% of the patients received carvedilol, at a mean dose of 5.8 mg/d. Therefore, the dosage of ACE inhibitor was comparatively low, and the use of β-blockade may not have been adequate. Additional studies are needed under full medication with ACE inhibitor and β-blockade. In addition, to verify the beneficial effect on late remodeling and post-infarct prognosis, further studies are needed.

Conclusions
The findings of the present study demonstrate that treatment with MRA combined with ACE inhibitor started immediately after revascularization can prevent LV remodeling and improve LVEF in patients with first anterior AMI. The mechanism of the beneficial effects of MRA is suggested to involve suppression of ALD extraction through the heart, attenuating the effect of cardiac collagen synthesis attributable to ALD.

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