ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Does Spironolactone Have a Dose-Dependent Effect on Left Ventricular Remodeling in Patients with Preserved Left Ventricular Function After an Acute Myocardial Infarction?

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SUMMARY

Aims: The aim of this study was to investigate the effects of spironolactone on left ventricular (LV) remodeling in patients with preserved LV function following acute myocardial infarction (AMI). **Methods and Results:** Successfully revascularized patients (n = 186) with acute ST elevation MI (STEMI) were included in the study. Patients were randomly divided into three groups, each of which was administered a different dose of spironolactone (12.5, 25 mg, or none). Echocardiography was performed within the first 3 days and at 6 months after MI. Echocardiography control was performed on 160 patients at a 6-month follow-up. The median left ventricular ejection fraction (LVEF) increased significantly in all groups, but no significant difference was observed between groups ($P = 0.13$). At the end of the sixth month, the myocardial performance index (MPI) had improved in each of the three groups, but no significant difference was found between groups ($F = 2.00$, $P = 0.15$). The mean LV peak systolic velocities (S_m) increased only in the control group during the follow-up period, but there is no significant difference between groups ($F = 1.79$, $P = 0.18$). The left ventricular end-systolic volume index (LVESVI) and the left ventricular end-diastolic volume index (LVEDVI) did not change significantly compared with the basal values between groups ($F = 0.05$, $P = 0.81$ and $F = 1.03$, $P = 0.31$, respectively). **Conclusion:** In conclusion, spironolactone dosages of up to 25 mg do not augment optimal medical treatment for LV remodeling in patients with preserved cardiac functions after AMI.

Introduction

The deterioration of cardiac performance after acute myocardial infarction (MI) induces the activation of neurohormonal systems, mainly the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) [1]. Due to the activation of these systems, pathological ventricular remodeling and progressive myocardial damage occur, and consequently heart failure develops, resulting in increased morbidity and mortality [2]. Now that the importance of aldosterone following MI is known, the need for the inhibition of neurohormonal mechanisms besides angiotensin-converting enzyme (ACE) has come to the forefront [3].

On the basis of the EPHESUS trial, aldosterone antagonists (class I) are recommended in combination with ACE inhibitors and beta-blockers for post-MI patients with left ventricular ejection fraction (LVEF) <40% [3,4]. Few studies have evaluated the efficacy of using spironolactone to treat patients with preserved LV function after MI [5,6]. In addition, past studies have produced insufficient data to establish the effectiveness of aldosterone antagonists in patients with LVEF >40% or the efficacy of different doses of aldosterone antagonists after MI. Therefore, we aimed to demonstrate the effects of different doses of spironolactone on LV function within a 6-month follow-up period using extensive echocardiography data from patients with preserved LV function following acute myocardial infarction (AMI).

Methods

Study Population

Patients with typical chest pain lasting for more than 30 min with ST segment elevation >1 mm in two or more consecutive precordial or inferior leads and diagnosed with first acute ST elevation MI (STEMI) who successfully underwent revascularization and had $\geq$40% LVEF were included in the study. Patients with very poor echocardiographic image quality, a history of MI, an

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extracardiac disease, and a life expectancy of <1 year, a planned early or urgent coronary bypass, heart failure of Killip classes III–IV, serum creatinine 2 mg/dL, or potassium 5.5 mEq/dL were not included in this study. Patients gave informed consent, and the study was approved by the local ethics committee.

Study Design and Protocol

This study was a prospective randomized controlled study. Once patients had undergone the revascularization process, they were admitted to the coronary intensive care unit and received standard treatment using beta-blockers, ACE inhibitors, and angiotensin receptor blockers (ARB). Patients were randomly divided into three groups, group 1, group 2, and control group, administered spironolactone to standard treatment at doses of 12.5, 25 mg, and none, respectively. The blood pressures of the patients were recorded during coronary intensive care follow-up. Echocardiography was performed 3 days and 6 months after MI. Follow-up appointments occurred 1 week, 1 month, 3 months, and 6 months after discharge. The target doses of beta-blockers and ACE inhibitors/ARBs were defined in accordance with the current best evidence (i.e., metoprolol 200 mg/day; carvedilol 50 mg/day; bisoprolol 10 mg/day; ramipril 10 mg/day; fosinopril 20 mg/day; perindopril 10 mg/day; valsartan 320 mg/day). Patients were investigated for potential side effects of spironolactone (gynecomastia, hyperkalemia, hypotension). Drug doses were decreased or stopped for patients who developed clinical or laboratory side effects. Philips Envisor-C echocardiography devices (Philips Medical Systems, Andover, MA, USA) were used to obtain the measurements. Conventional and tissue Doppler measurements were obtained using the standard apical 2- to 4-chamber view and parasternal long–short-axis images in the left lateral decubitus position. Measurements were recorded during expiratory breath-hold as an average value obtained from three consecutive pulse measurements.

Conventional Echocardiography

Two cardiologists, blinded to patient clinical history, performed the physical examinations, measured outcome variables, interpreted all echocardiograms, and verified LV volumetric analyses. Left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and LVEF were calculated using the biplane method of disks (modified Simpson's rule) in the apical 4- and 2-chamber views at end-systole and end-diastole. The left ventricular end-systolic volume index (LVESVI) and left ventricular end-diastolic volume index (LVEDVI) were then calculated as LVESV and LVEDV divided by body surface area. Measurements were obtained as the mean value from the apical 4- and 2-chamber views. Pulsed-wave Doppler of transmitral flow was used to assess global diastolic function, with the sample volume placed at the tips of the mitral leaflets in the apical 4-chamber view. The following Doppler indices were measured: peak early velocity (E), peak atrial velocity (A), and E-wave deceleration time (EDT). Left ventricular ejection time (ET), isovolumetric contraction time (ICT), and isovolumetric relaxation time (IRT) were calculated by locating the sample volume between the mitral and aortic valves in the apical 5-chamber image. Conventional myocardial performance index (MPI) was calculated using the formula '(ICT + IRT)/ET'.

Tissue Doppler Imaging

Measurements were obtained from five different areas, including the right ventricle, using apical 2- to 4-chamber images via the pulsed-wave tissue Doppler method (PWTD). PWTD records were obtained by placing the sample volume on the septal, lateral, anterior, and inferior walls of the mitral annulus. Right ventricle lateral wall records were taken from the apical 4-chamber view by placing the sample volume in the tricuspid annulus. The S_m, E_m, and A_m velocities and ICT, ET, and IRT values of each segment were measured. E/E_m ratios were calculated for each LV wall, and the mean E/E_m ratio was determined. The LV mean S_m was calculated as the sum of all LV wall S_m by dividing by 4. The tissue Doppler MPI was calculated using the formula (IRT + ICT)/ET.

Statistical Analysis

To calculate the target sample size for the present study, we used the available database of the study by Hayashi et al. [5]. We hypothesized that spironolactone would improve the LVEF by 15%. For a statistical power of 90% and a probability of a type I error of 0.05, we calculated that the sample size should be at least 35 patients per group. Statistical analysis was performed using IBM-SPSS version 19.0 software (SPSS, Inc., Armonk, NY, USA). Results are presented as mean ± standard deviation or median (interquartile range). The categorical variables are reported as counts and percentages and were compared using chi-square statistics. Continuous variables were compared within each group using Student's t-test or the Wilcoxon nonparametric statistic. To compare the means and ratios of basal echocardiography data between groups, single-direction ANOVA and chi-square tests were used. Differences between groups were analyzed using analysis of covariance with baseline echocardiographic values as covariates (6 month–baseline). The Bonferroni test was used as a *post hoc* test. A bilateral *P*-value of 0.05 was considered statistically significant for all the tests.

Results

A total of 186 patients were involved in the study initially. Echocardiography control was performed on 160 of the 186 patients at the end of the sixth month. The 26 patients who did not undergo echocardiography control were contacted by phone. Thirteen of the 26 had undergone an elective bypass at an external center. Of the remaining 13 patients, nine underwent revascularization (due to myocardial infarction, unstable angina, or in-stent restenosis), three experienced sudden deaths, and one had generalized intracerebral bleeding due to warfarin overdose caused by a left intraventricular thrombus.

Basal demographic data for the 160 patients who received echocardiography control are shown in Table 1. Most of the patients (84%) were men (mean age 56 ± 9). Of the patients, 18% had diabetes mellitus and 24% had hypertension. While 103 patients (64%) smoked, 15 (9%) quit smoking 2 months to 10 years before. All of the patients presented to the hospital with STEMI

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Table 1 Baseline clinical characteristics of 160 patients with 6 months' echocardiographic follow-up

Variable	Control (n = 56)	Group 1 (n = 50)	Group 2 (n = 54)	*P*-value
Age (years)	57 ± 11	54 ± 11	58 ± 9	0.073
Female (%)	20	14	15	0.491
Body mass index (kg/m²)	28.1 ± 5.4	26.3 ± 4.2	27.1 ± 3.9	0.412
Hypertension (%)	27	20	28	0.910
Smoking (%)	61	68	65	0.889
Diabetes mellitus (%)	20	16	17	0.680
Reperfusion type				0.486
Thrombolytic (%)	11	8	13	
Primary percutaneous coronary intervention (%)	89	92	87	
Symptom-Reperfusion time (hours)	4.9 ± 4.1	4.1 ± 2.4	3.9 ± 3.4	0.313
Infarct-related arterd				0.876
Left anterior descending (%)	59	56	57	
Circumflex (%)	9	12	9	
Right coronary (%)	32	32	34	
Killip class				0.890
Class 1 (%)	79	80	80	
Class 2 (%)	21	20	20	

for the first time. Primary percutaneous intervention was performed on 143 patients (89%), and thrombolysis was performed on 17 patients (11%) as a first-line reperfusion treatment. The time between the onset of symptoms and the beginning of the reperfusion process was 4.3 ± 3.3 h on average; for patients who underwent thrombolysis, the time was 2.6 ± 1.8 h. The mean time of spironolactone added to standard treatment was 18 h after revascularization. Of the patients who completed the study, 58% presented with anterior myocardial infarction and 42% presented with inferior and lateral myocardial infarction. There were no significant differences between the basal demographic characteristics of the different groups.

Following discharge, all of the patients received aspirin, beta-blockers, ACE inhibitors, or ARB. At the end of 6 months, only seven of the 160 patients were not using aspirin. Nine were not using beta-blockers, and 18 were not using ACE inhibitor/ARB (Table 2).

Basal echocardiographic values are shown in Table 3. The median LVEF value increased significantly in all groups during follow-up (group 1: 51.1% [interquartile range (IQR): 42–56]% to 53.5% [IQR: 47–58]%; $P = 0.03$, group 2: 49.1% [IQR: 40–55]% to 53.9% [IQR: 45–60]%; $P = 0.001$, control group: 50.1% [IQR: 41–55]% to 53.1% [IQR: 45–58]%; $P = 0.02$). However, no significant difference was demonstrated between groups ($P = 0.13$; Figure 1). The mean LV MPI, calculated using the tissue Doppler method, had also improved in each of the groups by the sixth month (group 1: 0.54 ± 0.11 to 0.49 ± 0.10; $P = 0.001$, group 2: 0.61 ± 0.16 to 0.52 ± 0.14; $P = 0.001$, control group: 0.61 ± 0.16 to 0.50 ± 0.11; $P < 0.001$). Again, no significant difference was observed between groups ($F = 2.00$, $P = 0.15$; Figure 2). The mean LV S_m significantly improved in the control group during follow-up (group 1: 8.6 ± 1.1 to 8.8 ± 1.1; $P = 0.24$, group 2: 8.2 ± 1.2 to 8.4 ± 1.2; $P = 0.41$, control group: 8.1 ± 1.3 to 8.6 ± 1.5; $P = 0.02$). However, no significant difference was demonstrated between groups ($F = 1.79$, $P = 0.18$).

Table 2 Medications of patients at 6 months' follow-up

Medications	Control (n = 56)	Group 1 (n = 50)	Group 2 (n = 54)	*P*-value
Aspirin (%)	54 (96)	47 (94)	52 (96)	0.968
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker (%)	46 (82)	48 (92)	50 (93)	0.084
Beta-blockers (%)	51 (91)	48 (96)	52 (96)	0.234

The mean systolic and diastolic volumes and indices did not change significantly compared to the basal values in any of the groups (Figures 3 and 4). The end-systolic and end-diastolic diameters were similarly preserved at the end of the sixth month. E/A, EDT, and E/E_m values were analyzed at the end of the sixth month, but no difference was found between groups. The differences between groups are shown in Table 4.

If LV remodeling is defined as a 20% increase in the LVEDV value, then LV remodeling was observed at the end of the sixth month in 28 of the 160 patients (17%) who received echocardiography control. Seventeen of these patients had anterior MI, and 12 did not receive spironolactone.

Of the patients' laboratory parameters, only potassium levels increased significantly in all the groups by the end of the sixth month. (group 1: 4.00 ± 0.41 to 4.48 ± 0.33 mEq/dL, $P < 0.001$; group 2: 4.08 ± 0.42 to 4.53 ± 0.36 mEq/dL, $P < 0.001$; control group: 4.15 ± 0.51 to 4.60 ± 0.46 mEq/dL, $P < 0.001$). However, no significant difference was demonstrated between groups ($F = 0.009$, $P = 0.926$). Spironolactone was discontinued in four patients due to gynecomastia. All of the patients who developed gynecomastia used 25 mg of spironolactone.

Interobserver measurement agreement values were 85.1% for LVEDV, 85.3% for LVESV, 85.2% for LVEF, 82.4% for MPI, and

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Table 3 Baseline echocardiographic characteristics of patients with 6 months' echocardiographic follow-up

Variable	Control (n = 56)	Group 1 (n = 50)	Group 2 (n = 54)	*P*-value
Left ventricular end-diastolic diameter (cm)	4.8 ± 0.40	4.79 ± 0.46	4.98 ± 0.47	0.148
Left ventricular end-systolic diameter (cm)	3.3 ± 0.47	3.2 ± 0.48	3.38 ± 0.56	0.208
Left ventricular end-diastolic volume (mL)	96.6 ± 25.2	98.2 ± 29.1	103.2 ± 27.4	0.143
Left ventricular end-systolic volume (mL)	49.7 ± 18.9	48.8 ± 18.4	55.1 ± 23.1	0.090
Left ventricular ejection fraction (%)	50.1 [41–55]	51.1 [42–56]	49.1 [40–55]	0.243
Left ventricular end-diastolic volume index (mL/m^2)	51.2 ± 13.8	51.6 ± 15.1	53.9 ± 15.3	0.230
Left ventricular end-systolic volume index (mL/m^2)	26.4 ± 10.4	25.6 ± 9.9	28.9 ± 15.3	0.130
Myocardial performance index	0.61 ± 0.16	0.54 ± 0.11	0.61 ± 0.16	0.071
Left ventricular mean peak systolic velocity (cm/s)	8.1 ± 1.3	8.6 ± 1.1	8.2 ± 1.2	0.185
E deceleration time (ms)	157.4 ± 41.1	158.9 ± 35.7	147.3 ± 40.3	0.394
E/A	1.01 ± 0.44	1.00 ± 0.32	1.20 ± 0.53	0.395
E/E_m	9.0 ± 3.2	7.9 ± 1.8	8.4 ± 3.0	0.157

Variables are expressed as mean ± standard deviation or median [interquartile range].

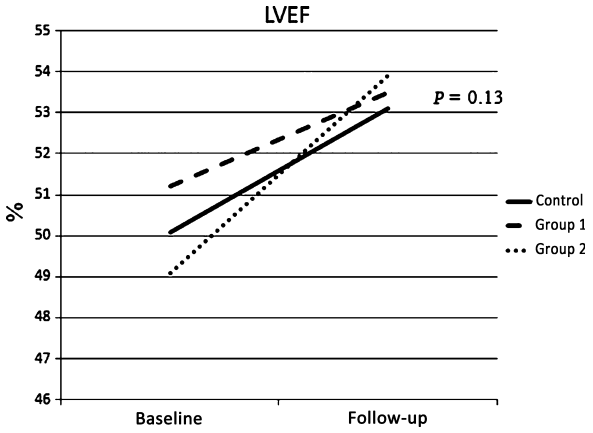

Figure 1 The median left ventricular ejection fraction increased significantly in all groups during 6 months' follow-up. There are no significant differences between the groups.

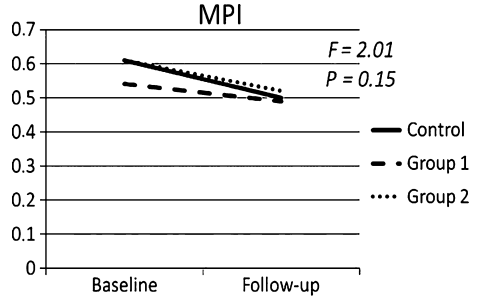

Figure 2 The mean myocardial performance index increased significantly in all groups during 6 months' follow-up. There are no significant differences between the groups.

86.3% for LV S_m. For intraobserver reproducibility, values were LVEDV 88.1%, LVESV 89.2%, LVEF 88.5%, MPI 85.3%, and LV S_m 90.1% agreement.

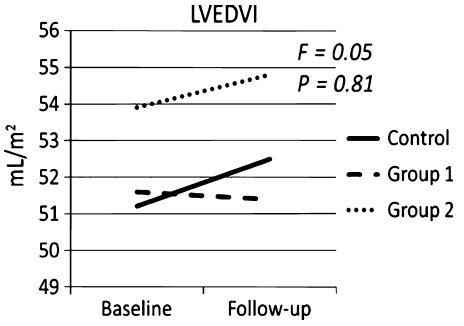

Figure 3 There are no significant differences in mean left ventricular end-diastolic volume index over the 6 months' period between the all groups.

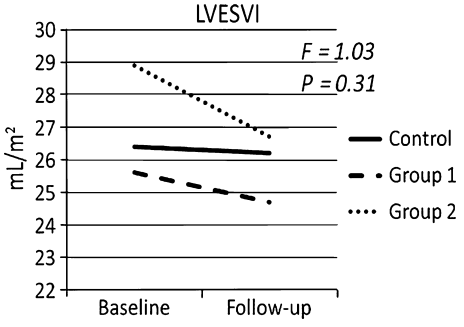

Figure 4 There are no significant differences in mean left ventricular end-systolic volume index over the 6 months' period between the all groups.

Discussion

The administration of spironolactone (up to a 25-mg dose) in addition to optimal anti-remodeling treatment at an early stage did not improve systolic and diastolic functions in STEMI patients who had successful early revascularization and preserved LV function within the 6-month follow-up period.

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Table 4 Differences in echocardiographic values between baseline and follow-up

Variable	Control (n = 56)	Group 1 (n = 50)	Group 2 (n = 54)	Covariate *P*-value
Left ventricular end-diastolic diameter (cm)	0.01 ± 0.42	−0.01 ± 0.43	0.03 ± 0.43	0.81
Left ventricular end-systolic diameter (cm)	−0.02 ± 0.50	−0.02 ± 0.44	0.01 ± 0.47	0.65
Left ventricular end-diastolic volume (mL)	2.58 ± 18.84	−0.34 ± 21.67	1.75 ± 26.54	0.79
Left ventricular end-systolic volume (mL)	−0.36 ± 15.58	−1.89 ± 11.41	−4.12 ± 21.86	0.30
Left ventricular ejection fraction (%)	2.56 [−2.1–10.1]	2.26 [−1.3–9.9]	4.53 [0.8–11.2]	0.13
Left ventricular end-diastolic volume index (mL/m^2)	1.30 ± 10.11	−0.11 ± 11.39	0.92 ± 13.71	0.81
Left ventricular end-systolic volume index (mL/m^2)	−0.26 ± 8.35	−0.87 ± 6.21	−2.25 ± 11.58	0.31
Myocardial performance index	−0.11 ± 0.13	−0.06 ± 0.10	−0.09 ± 0.15	0.15
Peak systolic velocity (cm/s)	0.42 ± 1.38	0.18 ± 0.98	0.14 ± 0.98	0.18
E deceleration time (ms)	20.61 ± 53.21	12.12 ± 34.33	28.17 ± 51.56	0.57
E/A	−0.17 ± 0.40	−0.02 ± 0.45	−0.07 ± 0.48	0.19
E/E_m	−1.05 ± 1.97	−0.12 ± 2.1	−0.69 ± 2.38	0.32

Variables are expressed as mean ± standard deviation or median [interquartile range].

The RAAS plays the most important role in the pathophysiology of LV remodeling after MI [7]. The first study showing the benefits of aldosterone antagonists in preventing aldosterone leaks was the RALES study conducted on patients with chronic heart failure [8]. After this study, the effect of eplerenone, a selective aldosterone antagonist, was evaluated in patients with LVEF below 40% after MI in the EPHESUS study [3].

Effective doses of aldosterone receptor blockers vary depending on the studies. Eplerenone was increased up to 50 mg/day in the EPHESUS study [3]. Spironolactone was used at doses of 25–50 mg/day in the RALES study [8]. In several other studies, 25–100 mg/day of spironolactone and 50 mg/day of eplerenone were used [5,9–11]. However, no studies have compared the efficacies of different dosages. One of the aims of our study was to examine the dose-dependent effects and side effects of spironolactone at lower doses; no differences were found between doses of up to 25 mg.

Studies of the effects of aldosterone antagonists on LV remodeling in post-MI patients with LVEF < 40% and chronic heart failure have produced controversial results [9–11]. In a study conducted by Hayashi et al. [5], spironolactone administration was randomized independent of LV systolic function and heart failure symptoms. Basal LVEF was 47% in their study. At 1-month follow-up, spironolactone had improved LVEF significantly. Thus, even though LV functions were preserved, their study suggested that spironolactone could have beneficial effects after MI [5]. However, the study's results were not verified echocardiographically. In the REVE study, basal LVEF was preserved at about 49% after infarction; after 1 year, LVEF showed significant improvement [6]. In this study, the aldosterone receptor antagonist usage ratio was very low, and the study did not effectively show that aldosterone receptor blockers improve systolic function after MI.

All patients who underwent revascularization, regardless of the MI type, were included in our study. The basal LVEF of our patients was 49%. There are many possible explanations for this high LVEF value, including (1) short revascularization time and short myocardium recovery time, (2) optimal medical treatment started at an early stage, (3) relatively late echocardiography (2.1 ± 0.9 days), (4) small inferior or lateral infarct size (observed in 42% of our patients), and/or (5) an artificially high calculated LVEF, determined using Simpson's rule, due to compensatory hyperkinesia of the noninfarcted segments after MI.

At the end of the sixth month, although significant improvement was observed in the systolic and diastolic functions of patients within each group, no difference was found between groups. In a study by Hayashi et al. [5], spironolactone had a positive effect on systolic function, but patient ACE inhibitor and beta-blocker usage was not optimal. Therefore, the contribution of spironolactone to systolic function may be more apparent due to the insufficient use of anti-remodeling medicine except spironolactone.

Hayashi et al. showed that an increase in LVEDV following MI was apparently depressed in the group of patients receiving spironolactone. They also found a significant decrease in LVESV in patients receiving spironolactone therapy and a significant increase in patients who were not [5]. They attributed the improvement in LV volumes to the anti-remodeling effects of spironolactone. As mentioned above, insufficient use of other anti-remodeling medicine might have caused the perceived positive effects of spironolactone. In the present study, the lack of increase in LV volumes or indices at the end of the sixth month could be explained by the use of optimal anti-remodeling treatment and successful early revascularization.

In many studies, LV remodeling was defined as a 20% increase in LVEDV [12–14]. If this definition is applied to REVE, 31% of the patients had LV remodeling at the end of the first year [6]. Bolognese et al. [15] stated that dilatation in the left ventricle following MI was proportionally related to poor prognosis. There were 28 patients (17%) in our study with a 20% LVEDV increase. Most of them (20 patients, 71%) had anterior MI, and 12 patients (42%) did not receive spironolactone. Anterior MI has been determined to be a predictor of LV remodeling [6,15]. Most of our patients who fit the LV remodeling definition had anterior MI (17 of 28, 61%) which supports this finding.

In our study, although serum potassium levels significantly increased in all patients during follow-up, no significant difference was determined between groups. Serum urea and creatinine levels did not increase in any group. We suggest that

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spironolactone and our other treatments are reliable in terms of renal functions.

Differences in terms of gynecomastia, another frequent side effect of aldosterone receptor blockers, could not be found between the eplerenone and placebo groups in EPHESUS [3]. In RALES, gynecomastia or breast pain developed in 10% of the spironolactone group (8). In the present study, gynecomastia and breast pain developed in 5% of the patients. All of the patients were in the group that received 25 mg. We hypothesize that the percentage was less than in the RALES trial because we did not increase the dose of spironolactone beyond 25 mg. The ratio would likely increase more if the dose were increased. Gynecomastia was the most important of the side effects requiring discontinuation of the medicine.

The present study has some limitations. Fibro-inflammatory parameters were not determined, and more precise imaging methods (such as cardiac magnetic resonance imaging, positron emission tomography) were not used for monitoring cardiac functions. However, comprehensive echocardiographic examinations were performed by two cardiologists blinded to previous patient data.

Conclusion

Remodeling after MI is still an important problem. Early revascularization and optimal medical treatment is key in improving cardiac functions for patients with AMI. According to the results of this study, doses of spironolactone up to 25 mg do not augment current optimal medical treatment for LV remodeling in patients with preserved cardiac functions after MI. However, there is still a need for studies that evaluate the effects of spironolactone in patients with preserved cardiac functions using doses of more than 25 mg more precise imaging techniques, and a greater number of patients.

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Conflict of Interest

The authors declare no conflict of interest.

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