Original Article

Relative Long-Term Effects of Spironolactone in Conjunction with an Angiotensin-Converting Enzyme Inhibitor on Left Ventricular Mass and Diastolic Function in Patients with Essential Hypertension

Atsuhisa SATO, Matsuhiko HAYASHI*, and Takao SARUTA*

It has been reported that treatment with an angiotensin-converting enzyme (ACE) inhibitor is not adequate to suppress aldosterone, and we previously demonstrated that adding spironolactone to an ACE inhibitor may have beneficial effects on left ventricular hypertrophy (LVH) in selected patients with essential hypertension (EH). We have extended our previous short-term study, and addressed the relative long-term clinical effects of spironolactone and an ACE inhibitor in patients with EH who have LVH. Twenty patients with EH and concomitant LVH participated in this study. Subjects were treated with either an ACE inhibitor alone (group 1: 10 patients) or an ACE inhibitor plus spironolactone at the dose of 25 mg (group 2: 10 patients) for 60 weeks. The baseline clinical and echocardiographic characteristics of the two groups were similar. Final values of blood pressure were also similar between the two groups. The LV mass index (LVMI) decreased significantly in both groups, but the extent of reduction was significantly greater in group 2 at 60 weeks. The early peak to atrial peak filling velocities ratio (E/A ratio) was significantly increased to a similar extent in both groups. Serum procollagen type III amino-terminal peptide (PIIINP) was significantly decreased in group 2, but not in group 1. In group 2, there was a statistically significant correlation between the changes in LVMI and PIIINP. In conclusion, adding spironolactone to therapy with an ACE inhibitor for 60 weeks may have beneficial effects in patients with EH and concomitant LVH. Our study strongly suggests the possibility that attenuation of the effects of cardiac aldosterone in patients with EH by treatment with spironolactone and an ACE inhibitor may become a new goal for the prevention and regression of cardiac hypertrophy.


Key Words: mineralocorticoid receptor antagonist, angiotensin-converting enzyme inhibitor, essential hypertension, cardiac hypertrophy

Introduction

Aldosterone is synthesized in the outer cortex of the adrenal gland and acts via epithelial mineralocorticoid receptors (MR) to promote unidirectional sodium and water transport (1). Recently, there has been increasing evidence that aldosterone exerts major cardiovascular effects via classical MR in nonepithelial tissues, such as brain and heart (2, 3). This nonepithelial role for aldosterone was underscored by the recent Randomized Aldactone Evaluation Study (RALES), which demonstrated that administration of the MR antagonist spironolactone conferred a 30% survival advantage to patients with congestive heart failure (4). Despite the availability of angiotensin-converting enzyme (ACE) inhibitors, unblocked aldosterone levels remain an important risk factor

From the Department of Internal Medicine, Mito Red Cross Hospital, Mito, Japan, and *Department of Internal Medicine, Keio University, Tokyo, Japan.

Address for Reprints: Atsuhisa Sato, M.D., Ph.D., Department of Internal Medicine, Mito Red Cross Hospital, 3–12–48 San-nomaru, Mito 310–0011, Japan. E-mail: atsu-sa@pb3.so-net.ne.jp

Received April 17, 2002; Accepted in revised form July 11, 2002.
for cardiovascular disease progression.

We have recently shown that plasma aldosterone levels tend to increase with the duration of ACE inhibitor treatment (aldosterone escape) (5), and that aldosterone escape may reverse the beneficial effects of ACE inhibition on left ventricular hypertrophy (LVH) in patients with essential hypertension (6). We have also demonstrated that adding spironolactone to an ACE inhibitor treatment may have beneficial effects, which may be explained at least in part by the limitation of extracellular collagen turnover, on LVH in selected patients with essential hypertension (7, 8). These studies suggest that treatment with an ACE inhibitor is not adequate to suppress aldosterone, whereas combination treatment with an ACE inhibitor and spironolactone will provide additional benefits in the prevention of cardiac hypertrophy, cardiac fibrosis, or both, even in selected patients with essential hypertension. In the present study, we extended our previous short-term studies (7, 8), and addressed the relative long-term clinical effects of spironolactone and an ACE inhibitor on left ventricular mass and diastolic function in patients with essential hypertension and concomitant LVH.

Patients and Methods

Subjects and Study Design
The study population consisted of 20 patients with essential hypertension (11 men and 9 women; mean age, 53 ± 12 years), 14 of whom were examined in our previous study (7, 8). Blood pressure and heart rate were measured as described previously (5–8). All patients were withdrawn from medication at least 2 weeks prior to their entry to this study. After obtaining informed consent, 20 patients were randomly assigned to two groups. They were started on an ACE inhibitor alone (trandolapril or enalapril) (10 patients; group 1) or spironolactone plus an ACE inhibitor (10 patients; group 2). During this study, the dose of spironolactone was constant (25 mg/day), and the dose of the ACE inhibitor was titrated based on changes in blood pressure, with all patients undergoing monthly check-ups throughout the study period (60 weeks). The study protocol was approved by the Committee on Medical Research Ethics of Mito Red Cross Hospital.

Biochemical Determinations
General biochemical parameters were measured by routine laboratory methods both before and after (at 60 weeks) treatment. Plasma renin activity and aldosterone concentration were measured using commercially available radioimmunoassay kits after the patients had been in the supine position for at least 30 min; sensitivity of the kits were 0.1–20 ng/ml/h (Renin Riabead, Dainabot Corp., Tokyo, Japan) and 25–1,600 pg/ml (SPAC-S Aldosterone Kit, Dai-ichi Radioisotope, Tokyo, Japan), respectively. Serum procollagen type III amino-terminal peptide (PIIINP) was also measured using a commercially available immunoradiometric assay kit that employs a monoclonal antibody to PIIINP with a normal range of 0.3–0.8 U/ml (7) (RIA-gnost PIIIP, CIS Diagnostic Corp., Chiba, Japan).

Echocardiographic Measurement
Echocardiographic studies were performed before and at 24, 48 and 60 weeks of treatment by the standard method using an SSA-380A echocardiograph with a 3.0 MHz transducer (Toshiba, Tokyo, Japan) according to the recommendations of the American Society of Echocardiography (9). LV mass was estimated from the formula of Devereux and Reichek (Penn convention) (10): LV mass (g) = 1.04 × [(LVDD + IVST + PWT) - (LVDD)] - 13.6, where LVDD is the LV end-diastolic dimension, IVST is the interventricular septal thickness, and PWT is the posterior wall thickness. The LV mass index (LVMI) was calculated for each subject by dividing the LV mass by the body surface area. All patients exhibited LVH defined as LVMI > 125 g/m² and/or IVST > 11 mm (11, 12). Early peak (E-peak) and atrial peak (A-peak) filling velocities were measured and their ratio (E/A ratio) was calculated. To reduce interobserver variability, all tracing were analyzed by a single expert cardiologist who was blinded to the clinical and biochemical data.

Statistical Analysis
Data are expressed as the mean ± SD, and the statistical significance between groups was investigated by two-tailed, unpaired t-test (Welch’s t-test). Changes in parameters in each group were analyzed by a single expert cardiologist who was blinded to the clinical and biochemical data.

Table 1. Baseline Characteristics of All Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1: ACE inhibitor alone</th>
<th>Group 2: ACE inhibitor + spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>5/5</td>
<td>6/4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>156 ± 15</td>
<td>164 ± 12</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>96 ± 8</td>
<td>98 ± 9</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>74 ± 3</td>
<td>72 ± 4</td>
</tr>
<tr>
<td>Na (mEq/l)</td>
<td>142.1 ± 1.5</td>
<td>142.5 ± 1.4</td>
</tr>
<tr>
<td>K (mEq/l)</td>
<td>4.2 ± 0.3</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>13.4 ± 2.0</td>
<td>12.8 ± 1.6</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.81 ± 0.22</td>
<td>0.79 ± 0.30</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>145 ± 44</td>
<td>142 ± 40</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>11.9 ± 2.3</td>
<td>12.2 ± 3.2</td>
</tr>
<tr>
<td>EF</td>
<td>0.69 ± 0.09</td>
<td>0.72 ± 0.10</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.84 ± 0.22</td>
<td>0.87 ± 0.27</td>
</tr>
</tbody>
</table>

All values are the mean ± SD. BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; LVMI, left ventricular mass index; IVST, interventricular septal thickness; EF, ejection fraction; E/A ratio, early peak to atrial peak filling velocities ratio.
group before and after treatment were compared by the two-
group paired *t*-test, with *p* values of *< 0.05* taken as signifi-
cant. Univariate correlation was established by Pearson’s
correlation coefficient.

## Results

### Baseline Characteristics

The baseline clinical, hemodynamic, echocardiographic and
biochemical characteristics of all patients are summarized in
Table 1. No significant differences in these parameters were
observed between the two groups. During treatment, 2 pa-
tients (1 patient in group 1 and 1 patient in group 2) com-
plained of cough, and dropped out of this study.

### Changes in Blood Pressure and Other Biochemical
Parameters

As shown in Fig. 1, time course changes in blood pressure
were similar in the two groups of patients. The final values of
blood pressure were similar in the 2 groups, and thus the anti-
hypertensive efficacy of the two treatments were comparable.

The doses of ACE inhibitor used in each group are shown in
Table 2, and were not significantly different between the
groups. Plasma renin activity increased significantly in both
groups, while plasma aldosterone concentration did not change
after treatment in either group (Table 3), and aldosterone es-
cape was seen in 4 patients in group 1 (44%). Heart rate, serum
potassium and magnesium remained unchanged throughout the
study (data not shown). In group 2, spironolactone did not
cause any side effect during the observation period.

### Table 3. Changes in Plasma Renin Activity (PRA) and Plasma Aldosterone Concentration (PAC) during Antihypertensive
Treatment

<table>
<thead>
<tr>
<th></th>
<th>Group 1 ACE inhibitor alone</th>
<th>Pre</th>
<th>Post 60 weeks</th>
<th>Group 2 ACE inhibitor + spironolactone</th>
<th>Pre</th>
<th>Post 60 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng/ml/h)</td>
<td>1.43 ± 1.05</td>
<td>3.52 ± 2.40 *</td>
<td>1.53 ± 1.00</td>
<td>3.98 ± 2.00 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAC (pg/ml)</td>
<td>88.5 ± 19.7</td>
<td>84.7 ± 19.4</td>
<td>83.9 ± 22.0</td>
<td>95.9 ± 23.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are the mean ± SD. *p < 0.05 vs. the value in pretreatment.
group 2, there was a statistically significant correlation between
dependently of blood pressure, and reflecting a direct effect of al-
derstitial and perivascular cardiac fibrosis in rats, indepen-
dentely of aldosterone. Administration of aldosterone with excess salt
has been shown to produce cardiac hypertrophy and both in-
tracellular and extracellular collagen turnover may also be attained by a spirono-
lactone combined with an ACE inhibitor was more cardio-
protective in terms of regression of LVH at 60 weeks of treat-
ment with an ACE inhibitor alone had beneficial effect on LVH in pa-
tients with essential hypertension. Nevertheless, we have previously
demonstrated that escaped aldosterone during treatment with an ACE inhibitor may reverse the benefical effect of the ACE inhibitor on LVH (6). And in a previous, short-term clinical study (8), we also showed that spironolactone at the dose of 25 mg may have beneficial effects on LVH in pa-
tients with essential hypertension who are receiving an ACE inhibitor. Our study suggested that attenuation of the effects of cardiac aldosterone in patients with essential hypertension whose plasma aldosterone levels are within the normal range, but escaped during ACE inhibitor treatment, may be-
come a new goal for the prevention and regression of cardiac fibrosis and hypertrophy. Nevertheless, there is no clear evi-
dence as to how long combined treatment with spironolac-
tone and an ACE inhibitor should be continued to obtain maximal cardiac effects.

In this study, we did not observe any differences between the two treatments in terms of cardioprotective effects at 24 weeks of treatment. The LV mass was significantly diminished, and the E/A ratio significantly increased to a similar extent in both groups. Although the final blood pressure values in the two groups were similar, treatment with spironolactone combined with an ACE inhibitor was more cardio-
protective in terms of regression of LVH at 60 weeks of treatment. Two aspects of these results appear worthy of analysis. The first involves aldosterone escape during treatment with an ACE inhibitor. In our previous study, we demonstrated that aldosterone escape did not participate in the antihypertensive effect, however, it did blunt the cardio-
protective effect of the ACE inhibitor (6). ACE inhibitors suppress aldosterone only for a short period, and aldosterone escape during treatment with an ACE inhibitor has been re-
ported to occur after at least 24 weeks of treatment (6, 15, 16). Therefore, considering the timing of aldosterone escape, it is possible that escaped aldosterone had direct deleterious effects, independent of blood pressure, on the heart via MR, and blunted the cardioprotective effects of the ACE inhibitor. This possibility is supported by the fact that although treat-
ment with an ACE inhibitor alone had beneficial effect on

Changes in LVMI, E/A Ratio and Serum PIIINP Value
during Antihypertensive Treatment

The changes in LVMI and IVST did not differ significantly between group 1 and group 2 at 24 weeks of treatment. After 48 weeks, however, the extent of reduction was significantly greater in group 2 (125 ± 28 g/m² in group 1 vs. 110 ± 25 g/m² in group 2), and this difference was still apparent at 60 weeks (Table 4). The E/A ratio before treatment was similar in both groups, and was significantly increased after 60 weeks of treat-
ment in both groups. There was no statistically significant dif-
ference between both treatment regimens at 60 weeks (Table 4). Serum PIIINP decreased significantly in group 2 (from 0.67 ± 0.24 to 0.50 ± 0.12 U/ml), but not in group 1 (Fig. 2). In group 2, there was a statistically significant correlation between the changes in LVMI and PIIINP (r = 0.66, p = 0.04) There were no correlations between serum PIIINP levels and blood pressure (data not shown).

Discussion

The present study suggests that treatment with spironolactone combined with an ACE inhibitor may be clinically use-
ful and safe for patients with essential hypertension espe-
cially for those who have LVH. Treatment with spironolactone
was associated with a reduction in serum levels of PIIINP and a decrease of LVMI. Significant inhibition of extracellu-
lar collagen turnover may also be attained by a spironolac-
tone and ACE inhibitor treatment.

ACE inhibitors have been shown to be cardioprotective and to significantly reduce the morbidity and mortality of pa-
tients with cardiovascular diseases; however, recent studies have shown that one of the drawbacks of ACE inhibitors may be their inability to induce a sustained suppression of aldosterone. Administration of aldosterone with excess salt has been shown to produce cardiac hypertrophy and both in-
trstitial and perivascular cardiac fibrosis in rats, independ-
ently of blood pressure, and reflecting a direct effect of al-
derosterone on the heart mediated by cardiac MR (13, 14). In a clinical setting, the potentially harmful effects of residual, escaped aldosterone during ACE inhibitor treatment have been demonstrated in patients with congestive heart failure

by the RALES trial (4). In contrast to the patients with con-
gestive heart failure, plasma aldosterone levels are only marginally elevated or within the normal range in most patients with essential hypertension. Nevertheless, we have previously

demonstrated that escaped aldosterone during treatment with an ACE inhibitor may reverse the benefical effect of the ACE inhibitor on LVH (6). And in a previous, short-term clinical study (8), we also showed that spironolactone at the dose of 25 mg may have beneficial effects on LVH in pa-
tients with essential hypertension who are receiving an ACE inhibitor. Our study suggested that attenuation of the effects of cardiac aldosterone in patients with essential hypertension whose plasma aldosterone levels are within the normal range, but escaped during ACE inhibitor treatment, may be-
come a new goal for the prevention and regression of cardiac fibrosis and hypertrophy. Nevertheless, there is no clear evi-
dence as to how long combined treatment with spironolac-
tone and an ACE inhibitor should be continued to obtain maximal cardiac effects.

Changes in LVMI, E/A Ratio and Serum PIIINP Value
during Antihypertensive Treatment

<table>
<thead>
<tr>
<th>Table 4. Changes in Left Ventricular Mass Index (LVMI) and Early Peak (E-Peak) to Atrial Peak (A-Peak) Filling Velocities Ratio (E/A Ratio) during Antihypertensive Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>ACE inhibitor alone</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
</tr>
<tr>
<td>E/A ratio</td>
</tr>
<tr>
<td>Peak E (m/s)</td>
</tr>
<tr>
<td>Peak A (m/s)</td>
</tr>
</tbody>
</table>

All values are the mean ± SD. * p < 0.05 vs. the value in pretreatment, + p < 0.05 vs. group 1.
LVH in this study, LVM1 values at 60 weeks of treatment did not change significantly from those at 24 weeks. Given the dose of spironolactone used (25 mg daily), which is generally considered suboptimal for reduction of blood pressure, the effectiveness of spironolactone in this study may have been due to a blockade of the direct cardiac effects of escaped aldosterone, rather than to a hemodynamic effect.

Secondary, classical effects of aldosterone on epithelial tissues, such as effects on ion transport, appear within 1 h and reach plateau levels after 3 to 6 h of constant exposure. In contrast, the effects of aldosterone with excess salt on cardiac collagen mRNA levels require 1 to 2 weeks to appear; a longer period is required for maximal effects (17). Such differences in the time course of action may reflect inherent differences in the properties of non-epithelial and epithelial MR. Given the results in this study, treatment with spironolactone may thus need to be continued for relative long periods before its effect reaches plateau levels.

Diastolic dysfunction is a common abnormality in mild to moderate hypertension and is frequently seen in the presence of LVH. Long-term treatment of hypertension has been shown to improve diastolic function (18). However, the structural adaptation of LV in hypertension is considered to be modified not only by pressure overload but also by humoral factors. Interstitial fibrosis in the heart can also influence diastolic function; for this reason, we first thought that spironolactone improved diastolic dysfunction more effectively than treatment with an ACE inhibitor alone. In this study, the E/A ratio improved in both groups to a similar extent, which suggests that lowering blood pressure is a more stronger determinant of improvement of diastolic dysfunction than plasma aldosterone levels. Nevertheless, given the severe cardiac fibrosis observed in the experimental aldosterone with excess salt model, there is still a possibility that aldosterone play a role in diastolic function, independent of blood pressure, in patients with essential hypertension.

Fibrillar type III and I collagen constitute the majority of total collagen found in the myocardium (19). Serum PIIINP levels have been proposed as a useful marker of collagen type III synthesis (20). The present study showed that treatment with spironolactone was associated with a reduction in serum levels of PIIINP and a decrease of LVM1, and suggests that, in patients with essential hypertension, major inhibition of extracellular collagen turnover can be attained by adding spironolactone to the treatment protocol. The clinical meaning of the changes in serum PIIINP within the normal range awaits for further studies. Finally, because our data were obtained in a small sample size, larger and longer studies may provide further clinical evidence to confirm our findings. However, in addition to our previous study (8), we confirmed that although hyperkalemia has been frequently associated with the combination of an ACE inhibitor and spironolactone, there was no evidence of hyperkalemia in this study, probably because of the low dose of spironolactone.

In conclusion, adding spironolactone to therapy with an ACE inhibitor for 60 weeks may have beneficial effects in patients with essential hypertension, especially in those who have LVH. Our study strongly suggests the possibility that attenuation of the effects of cardiac aldosterone in patients with essential hypertension by complete inhibition of the renin-angiotensin-aldosterone system with spironolactone and an ACE inhibitor may become a new goal for the prevention and regression of cardiac fibrosis and hypertrophy.

Acknowledgements

The authors would like to thank Professor Bertram Pitt (University of Michigan Hospital, Ann Arbor, MI, USA) for critical reading of the manuscript.

References

11. Devereux RB: Detection of left ventricular hypertrophy by M-mode echocardiography: anatomic validation, standard-