The role of spironolactone in the metabolism of serum type I collagen in elderly patients with atrial fibrillation


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Abstract. – OBJECTIVE: This study aimed to explore the possible mechanism of spironolactone in reduction of atrial fibrosis in elderly patients with atrial fibrillation.

PATIENTS AND METHODS: 67 patients with atrial fibrillation and 30 matching patients with sinus rhythm were included into this study, in which the former patients were randomly divided into the conventional treatment group (33 cases) and spironolactone (20 mg/d) treatment group (34 cases). They underwent follow-ups for 6 months. The levels of serum aldosterone, PICP (propeptide of type I procollagen) and CITP (carboxy-terminal cross-linking telopeptide of type I collagen) were determined before and after treatment.

RESULTS: The concentrations of serum PICP, CITP and aldosterone and left atrial size in the atrial fibrillation group were all higher than the control group (t values were 7.982, 5.950, 9.309, 9.050, respectively, \( p < 0.01 \)), with a significant statistical difference. The concentrations of serum PICP and aldosterone were both positively correlated to the left atrial size in the atrial fibrillation group (r values were 0.302 and 0.369, respectively). The levels of serum aldosterone and PICP after treatment were both decreased compared to those before treatment in the spironolactone treatment group and conventional treatment group, especially in the spironolactone treatment group. There were statistical differences in the levels of serum aldosterone and PICP after treatment between the two groups (t values were 2.872 and 3.054, respectively, \( p < 0.01 \)).

CONCLUSIONS: Spironolactone could reduce the levels of serum aldosterone and PICP in patients with atrial fibrillation, so as to reduce the atrial fibrosis and delay the occurrence and development of atrial fibrillation.

Key Words:
The elderly, Atrial fibrillation, Spironolactone, Aldosterone, Serum PICP, Serum.

Introduction

Atrial fibrillation (AF) was a common and complicated arrhythmia in clinical, especially in the elderly. With the growth of ages, the morbidity of this disease was gradually raised. The continuous AF often caused heart failure, cerebral embolism and other serious complications, with a higher mortality and morbidity. The pathogenesis was very complicated. It had been found that the atrial electrical remodeling and structural remodeling were closely related to the occurrence of AF\(^2\), and the structural remodeling was the important reason for the occurrence and maintain of AF\(^3\). The fibrosis of atrial muscle in the structural remodeling center was considered to be the structural foundation for the occurrence of AF\(^4\). More and more evidences indicated that the activation of aldosterone receptor was the important factors to promote the progress of atrial fibrosis and atrial fibrillation\(^5\). In addition, the aldosterone receptor antagonist could effectively reduce the occurrence of atrial fibrosis and atrial fibrillation in the animal model center\(^6\), which draws more and more attention as a potential treatment way of atrial fibrillation. In this study, the serum aldosterone level and the levels of serum carboxy-terminal propeptide of type I procollagen (PICP) and carboxy-terminal cross-linking telopeptide of type I collagen (CITP) in elderly patients with atrial fibrillation were determined to discuss the change of serum aldosterone level and the role of spironolactone, the aldosterone receptor antagonist, in inhibition of atrial fibrosis and atrial fibrillation.

Patients and Methods

Patients

67 elderly patients with atrial fibrillation were admitted into our Hospital from 2009 to 2010, which were with the duration for more than a half year. Wherein, 42 males and 25 females, aged from 65 to 90 years old, on the average of (71.0 ± 8.5) years old, were all the out-patients.
and hospitalized patients in the Gerontology Department. Another 30 patients were without previous histories of atrial fibrillation. The patients with sinus rhythm according to the current ECG and 24-hour dynamic ECG were as control, which were matched with the atrial fibrillation group in gender, age, coronary heart disease, hypertension, diabetes mellitus, cardiovascular disease and other basic lesions. And 67 elderly patients with atrial fibrillation were randomly divided into conventional treatment group (33 cases) and spironolactone treatment group (34 cases), with no differences in gender, age, body mass index, etc., between the two groups. The clinical characteristics of the two groups of patients were shown in Table I. In order to avoid being affected by drugs, patients underwent treatment for 6 months after wash-out period for one week. Patients with heart failure, acute coronary syndrome, rheumatic heart disease, thyroid dysfunction, liver/kidney failure, chronic lung disease, malignant tumor as well as those to be given surgeries and with histories of stroke in recent three months were excluded. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Third Hospital of Hebei Medical University. Written informed consent was obtained from all participants.

**Methods**

The spironolactone treatment group underwent treatment of calcium ion antagonists, β-receptor blockers, (ACEI) or (ARB) and other drugs, as well as a small dose of additional spironolactone (20 mg/d) for 6 months. The patients underwent Doppler echocardiography before treatment and after treatment for 6 months respectively to measure the left atrial size. They underwent monthly serum potassium test to learn about whether the serum potassium was increased. 5 ml of fasting venous blood in patients before treatment and after treatment for 6 months were taken respectively and centrifuged to obtain the serum, which were saved at −20°C for further test. Measurement of biochemical indicators: aldosterone (ALD) was measured by radioimmunoassay according to the kit instruction, provided by the Northern Institute of Immunological Reagents, China Isotope Company. PICP and CITP titers were measured by radioimmunoassay according to the kit instruction, bought from Finland Orion Diagnostica Company, Espoo, Finland.
**Statistical Analysis**

SPSS 10.0 software (SPSS Inc., Chicago, IL, USA) was used to process data. The measurement data were presented as mean ± standard deviation (± s). t test was used for comparison between groups. The enumeration data were measured using ² inspection. The linear correlation analysis was used for correlation between the two variables, and p < 0.05 was presented as a statistical difference.

**Results**

The serum concentrations of PICP, CITP and aldosterone as well as the left atrial size in the atrial fibrillation group were higher than those in the control group (t values were 7.982, 5.950, 9.309, 9.050, respectively, p < 0.01), with a significantly statistical difference. According to the correlation analysis, the serum aldosterone in the atrial fibrillation group was positively correlated to the left atrial size (r = 0.302, p < 0.05), serum PICP concentration was positively correlated to the left atrial size (r = 0.369, p < 0.01), and serum aldosterone concentration was positively correlated to the serum PICP concentration (r = 0.428, p < 0.01, Table II).

After treatment, the serum PICP and aldosterone levels in both conventional treatment group and spironolactone treatment group were significantly decreased, especially in the spironolactone treatment group, with a statistical difference between the two groups after treatment (t values were 2.872 and 3.054 respectively, p < 0.01). There was no statistical difference in serum CITP level and left atrial size between the two groups after treatment (t values were 1.003 and 0.324 respectively, p > 0.05, Table III). Three patients in spironolactone treatment group were transferred to paroxysmal atrial fibrillation. There was no increased potassium found during the treatment.

**Discussion**

Many studies showed that atrial remodeling, especially the structural reconstruction with atrial fibrosis as the center, was the core of the occurrence and development of atrial fibrillation and the most important structural foundation to maintain atrial fibrillation. Many evidences had confirmed RAAS (rennin-angiotensin-aldosterone system) activation was closely related to the structural reconstruction of atrial fibrillation, and multiple clinical trials showed that ACEI (ACE inhibitors) and ARB (Angiotensin II receptor blocker) could reduce the incidence of atrial fibrillation. Since RAAS activation was simultaneously accompanied by the increase of aldosterone synthesis, and the strong aldosterone-induced myocardial fibrosis had been found in a lot of animal experiments and clinical researches, the relationship of aldosterone and atrial fibrillation had drawn great attention. The domestic studies had confirmed that the aldosterone level in the atrial muscle tissue was significantly increased in patients with atrial fibrillation, the gene expression of key enzyme CYP11B for aldosterone synthesis was significantly unregulated in the atrial muscle compared to those with sinus rhythm, and the mRNA and protein expression of mineralocorticoid receptor in the atrial muscle tissue in patients with atrial fibrillation were significantly increased compared to those with sinus rhythm. The foreign studies had found that the incidence of atrial fibrillation in patients with primary aldosteronism was 12 times as much as those patients matched in gender, age and blood pressure level. This study had also confirmed that the serum aldosterone levels in patients with atrial fibrillation were higher than those patients with sinus rhythm and matched in the gender, age and blood pressure level, consistent with the literatures findings.

Atrial structural reconstruction was centered in atrial fibrosis, whose main pathological perfor-

<table>
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<tr>
<th>Groups</th>
<th>Cases</th>
<th>Serum PICP (ug/l)</th>
<th>Serum CITP (ug/l)</th>
<th>Serum aldosterone (pg/ml)</th>
<th>Left atrial diameter (mm)</th>
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</thead>
<tbody>
<tr>
<td>Conventional treatment group</td>
<td>67</td>
<td>140.38 ± 29.45</td>
<td>3.95 ± 0.56</td>
<td>376.3 ± 78.7</td>
<td>42.6 ± 5.0</td>
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<tr>
<td>Spironolactone treatment group</td>
<td>30</td>
<td>92.21 ± 22.32</td>
<td>3.21 ± 0.58</td>
<td>226.3 ± 59.4</td>
<td>33.6 ± 3.2</td>
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<tr>
<td>Statistic</td>
<td></td>
<td>7.982</td>
<td>5.950</td>
<td>9.309</td>
<td>9.050</td>
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<tr>
<td>p value</td>
<td></td>
<td>&lt; 0.01</td>
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The increased and disordered collagen deposition was the increased and disordered collagen deposition. The main composition of myocardial extracellular matrix was collagen, 85% of which was the type I collagen. The serum carboxy-terminal propeptide of type I procollagen (PICP) was the serological marker of extracellular synthesis of type I collagen, which was correlated to cardiac collagen deposition 14. CITP was the serum carboxy-terminal propeptide of type I procollagen, which was formed through the hydrolysis of type I collagen fibers by matrix metalloproteinase, and the measurement of serum CITP level could be used as the serological marker of extracellular degradation of type I collagen 15,16.

Polyakov et al 17 found that the expression of type I collagen in atrial muscle tissue in patients with atrial fibrillation was higher than those with sinus rhythm. Kallerqis et al 18 found that the serum PICP and CITP levels in patients with isolated atrial fibrillation were higher than those control patients with sinus rhythm. This study also confirmed that the serum PICP and CITP levels in patients with atrial fibrillation were higher than those patients with sinus rhythm and matched in gender, age and blood pressure level, consistent with the literatures.

Large evidences indicated that mineralocorticoid receptor activation was an important factor of the occurrence and development of atrial fibrosis and atrial fibrillation. Aldosterone was combined with the mineralocorticoid receptor to activate the RAS system and play a strong myocardial fibrosis effect 19. Aldosterone receptor antagonist could reduce the occurrence of atrial fibrillation and fibrillation, which was referred to paroxysmal atrial fibrillation. Rats with myocardial fibrosis were given simple spironolactone, angiotensin-converting-enzyme inhibitor and receptor inhibitor respectively by Milliez et al 20, which showed that the myocardial fibrosis was significantly reduced only in rats given spironolactone, indicating the role of aldosterone in myocardial fibrosis and the important role of spironolactone, the aldosterone receptor antagonist, in myocardial fibrosis treatment.

This research showed that after the treatment with small dose of spironolactone for 6 months in patients with atrial fibrillation, the serum PICP and aldosterone levels were significantly decreased, and aldosterone levels were significantly increased in patients with atrial fibrillation. The serum PICP and aldosterone levels in patients with atrial fibrillation were significantly higher than those with sinus rhythm. Therefore, the use of spironolactone as a treatment for atrial fibrillation is promising. The serum PICP and CITP levels were significantly higher in patients with atrial fibrillation than those with sinus rhythm, and the serum aldosterone level was also higher in patients with atrial fibrillation than those with sinus rhythm. This study also found that the serum PICP and CITP levels were significantly lower in patients with atrial fibrillation than those with sinus rhythm, and the serum aldosterone level was also lower in patients with atrial fibrillation than those with sinus rhythm.

### Table III. Comparison of concentrations of serum PICP, CITP and aldosterone and left atrial size before and after treatment between the two group (x ± s).

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</thead>
<tbody>
<tr>
<td>Conventional treatment group</td>
<td>34</td>
<td>140.31 ± 28.07</td>
<td>105.12 ± 25.34</td>
<td>3.92 ± 0.56</td>
<td>3.72 ± 0.50</td>
<td>378.3 ± 78.1</td>
<td>266.8 ± 69.3</td>
<td>42.4 ± 5.1</td>
<td>41.5 ± 4.4</td>
</tr>
<tr>
<td>Spironolactone treatment group</td>
<td>33</td>
<td>140.47 ± 29.45</td>
<td>122.41 ± 24.94</td>
<td>3.96 ± 0.58</td>
<td>3.85 ± 0.56</td>
<td>372.4 ± 79.1</td>
<td>319.3 ± 71.4</td>
<td>42.8 ± 4.9</td>
<td>41.9 ± 4.7</td>
</tr>
<tr>
<td>p value</td>
<td>&gt; 0.05</td>
<td>&lt; 0.01</td>
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Conventional treatment group. This study also found that there were no changes of left atrium diameter and serum CITP level in patients before and after treatment, which was considered to be related to the short observation time, and the specific mechanism remained to be further discussed. The serum potassium was detected in the normal range during the treatment, without increased potassium found in patients.

Conclusions

Spironolactone, the aldosterone receptor antagonist, could reduce the serum aldosterone and PICP concentrations in patients with atrial fibrillation to reduce the synthesis of type I collagen and reduce atrial fibrosis and atrial remodeling, so as to delay the occurrence and development of atrial fibrillation, which was the safe and effective drug to reduce atrial remodeling and improve the prognosis in patients with atrial fibrillation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References