Journal of Cardiology 63 (2014) 205–210

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

# Long-term effects of irbesartan on plasma aldosterone concentration and left atrial volume in hypertensive patients

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ARTICLE INFO

*Article history:*
Received 19 June 2013
Received in revised form 30 July 2013
Accepted 2 August 2013
Available online 21 September 2013

*Keywords:*
Hypertension
Aldosterone
Left atrial volume
Angiotensin type II receptor blocking drugs
Calcium channel blocking drugs

ABSTRACT

*Background:* Plasma aldosterone concentration (PAC) is related to cardiac remodeling in patients with hypertension. However, we do not know the detailed relationship between changes in PAC and regression of left atrial (LA) volume following long-term treatment with angiotensin II receptor blocker (ARB) or calcium-channel blocker (CCB).
*Objective:* The aim of this study was to investigate the effects of anti-hypertensive monotherapy, an ARB irbesartan or a CCB amlodipine, on PAC and LA reverse remodeling in hypertensive patients.
*Methods:* A total of 48 patients with untreated hypertension were randomly assigned to irbesartan (ARB group, $n = 26$) and amlodipine (CCB group, $n = 22$). We examined the correlation between LA volume index (LAVI) and other echocardiographic parameters or PAC ($n = 40$) at the baseline and after 12 months of treatment.
*Results:* After 12 months, blood pressure (BP) decreased similarly in both groups. LAVI and PAC significantly decreased in the ARB group, but not in the CCB group ($-16 \pm 8\%$ vs. $22 \pm 9\%$, $p < 0.01$, $-16 \pm 9\%$ vs. $11 \pm 9\%$, $p < 0.05$). Larger %-decrease in PAC was associated with larger %-reduction of LAVI in the ARB group ($r = 0.54$, $p < 0.05$), but not in the CCB group.
*Conclusions:* While BP reduction was similar between the two groups, decrease in LA volume was larger in the ARB group than in the CCB group. Decrease in LA volume was larger in patients with a greater decrease in PAC than in those with smaller decrease in PAC. ARB may facilitate reverse remodeling of LA through decreases in PAC in hypertensive patients.


## Introduction

Hypertension leads to adverse cardiac remodeling, such as left atrial (LA) enlargement, left ventricular (LV) hypertrophy, and cardiac fibrosis [1,2]. Cardiac remodeling is associated with increased morbidity and mortality due to subsequent heart failure [3]. Clinical studies have shown that inhibiting the renin–aldosterone system using angiotensin-converting enzyme (ACE) inhibitors or angiotensin type II receptor blockers (ARB) induced cardiac reverse remodeling [4–6]. Moreover, plasma aldosterone has a crucial role in development of cardiac remodeling [7]. We previously reported that the inhibition of plasma aldosterone works as a contributor to regression of LV mass in hypertensive patients following long-term treatment with ARB or calcium channel blocker (CCB) [8].

LA enlargement [9–13] is strongly correlated with atrial fibrillation and mortality in hypertensive patients. Further, LA reverse remodeling by the ARB losartan was reported to be associated with absence of new onset of atrial fibrillation [5]. However, it is unclear whether ARB or CCB could decrease plasma aldosterone concentration (PAC) and LA volume in patients with untreated hypertension. Thus, the aim of this study was to investigate the impact of decrease

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http://dx.doi.org/10.1016/j.jjcc.2013.08.004

in PAC as a contributor to regression of LA volume index in hypertensive patients following long-term treatment with ARB or CCB.

## Materials and methods

### Subjects

We enrolled 48 patients with untreated hypertension who presented to the outpatient clinic of Hyogo College of Medicine between January 2010 and December 2012. Patients were included in the study if they met the following criteria: 20 years of age or older, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 140 and 90 mmHg or over. Patients were excluded if they had secondary hypertension of any cause, angina pectoris or acute coronary artery disease, current or recent history of congestive heart failure, valvular heart diseases, cardiac arrhythmias, renal dysfunction (serum creatinine level over 2.0 mg/dl), or diabetes mellitus. Informed consent was obtained from all patients, and the study was designed to comply with the ethical principles of our institution. Eligible patients were randomly assigned in a 1:1 ratio to receive either amlodipine 2.5 mg daily (CCB group) or irbesartan 100 mg daily (ARB group). Target SBP and DBP were below 140 and 90 mmHg, respectively. If blood pressure reduction did not achieve the target level after 4 weeks, the dose of amlodipine was doubled to 5 mg, and irbesartan to 200 mg. The third and fourth steps of treatment included the addition of a thiazide and/or alpha-blocker.

### Blood chemistry

Among 48 subjects, we could collect blood samples for PAC and B-type natriuretic peptide (BNP) measurement from 20 patients each in the ARB and CCB groups. Blood samples ($n = 40$) were taken between 09.00 and 11.00 h and were immediately placed on ice and centrifuged within 1 h. The specimens were stored at −80 °C until analysis. PAC was measured with a radioimmunoassay kit (SPAC-S Aldosterone Kit; Otsuka Pharmaceutical Co., Ltd., TFB, Tokyo, Japan). Plasma BNP concentration was measured with a Shionoria BNP kit (Shionogi Inc., Tokyo, Japan).

### Echocardiographic studies

Transthoracic echocardiography was performed at baseline and 12 months after treatment in all patients. Echocardiography was recorded with iE33 (Philips Medical Systems, Bothell, WA, USA). A standard, comprehensive, M-mode, 2-dimensional echocardiography and Doppler study were conducted according to the guideline of the American Society of Echocardiography [14]. LA volume was calculated with a formula using an ellipsoid model and was indexed to the body surface area, i.e. LAVI [15]. LV mass index (LVMI) and relative wall thickness (RWT) were measured by the method described previously [8]. Peak velocities of early diastolic phase ($E$) and late diastolic phase ($A$) of mitral inflow, and the $E/A$ ratio were measured by pulsed-wave Doppler echocardiography with the sample volume between mitral leaflet tips. Mitral annulus velocities ($E'$) and $E/E'$ ratio were measured at the septal annulus by tissue Doppler imaging.

### Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki after receiving approval from the institutional review board of Hyogo College of Medicine. All subjects provided written informed consent prior to participation.

### Statistical analysis

The primary outcomes included changes in PAC and LA volume in hypertensive patients following long-term treatment with amlodipine or irbesartan. Continuous data are presented as mean (±SD). We compared values at baseline and after treatment using paired $t$-test. The correlations between LAVI and PAC, LVMI and $E/E'$ were examined using linear regression analysis. A $p$-value less than 0.05 was considered significant. Statistical computations were performed with JMP version 10.0.1 (SAS Institute, Inc., Cary, NC, USA).

## Results

### Patient characteristics

There were 35 men and 13 women with a mean age of 62 years. The final dose of amlodipine was 145 ± 57 mg/day and that of irbesartan was 4.4 ± 1.2 mg/day. Thiazide indapamide 1 mg was added to the basal medications in two patients in the ARB group and three patients in the CCB group and the alpha blocker doxazosin 1 mg was added to three patients in the CCB group and no patients in the ARB group. Baseline characteristics were similar in both groups of patients (Table 1).

### Changes in blood pressure and echocardiographic parameters and humoral factors

After 12 months of treatment, SBP, DBP, and LVMI decreased similarly in both ARB and CCB groups. Heart rate (HR), $E/A$, deceleration time (DT) of $E$ wave and natural logarithm of brain natriuretic peptide (Ln BNP) did not change in either group. The LA dimension (LAD) tended to decrease in the ARB group, and tended to increase in the CCB group. The LAVI, $E/E'$, and PAC significantly decreased in the ARB group, but not in the CCB group. The $E$ and $A$ were significantly increased in the CCB group, but not in the ARB group (Table 2).

**Table 1**
Baseline characteristics of study subjects.

| | ARB ($n = 26$) | CCB ($n = 22$) | $p$-Value |
|---|---|---|---|
| Age (years) | 63 ± 12 | 60 ± 13 | 0.68 |
| Sex (female/male) | 7F, 19M | 6F, 16M | 0.32 |
| BMI | 24 ± 3 | 24 ± 4 | 0.17 |
| SBP (mmHg) | 161 ± 20 | 162 ± 19 | 0.29 |
| DBP (mmHg) | 92 ± 15 | 94 ± 12 | 0.60 |
| HR (bpm) | 69 ± 12 | 66 ± 17 | 0.52 |
| LAD (mm) | 36 ± 6 | 36 ± 5 | 0.92 |
| LAVI (ml/m$^2$) | 24 ± 7 | 22 ± 6 | 0.26 |
| LVEDD (mm) | 48 ± 5 | 49 ± 4 | 0.60 |
| LVESD (mm) | 30 ± 5 | 29 ± 7 | 0.47 |
| RWT | 0.40 ± 0.06 | 0.41 ± 0.01 | 0.51 |
| LVEF (%) | 67 ± 7 | 67 ± 5 | 0.45 |
| LVMI (g/m$^2$) | 96 ± 26 | 102 ± 16 | 0.45 |
| Comorbidity | | | |
| Dyslipidemia (%) | 8 (31) | 10 (45) | 0.29 |
| Smoking (%) | 2 (7) | 1 (5) | 0.65 |
| Baseline medication | | | |
| Statin $n$ (%) | 4 (15) | 7 (32) | 0.94 |

ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LAD, left atrial diameter; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.