Endothelial Dysfunction Is Related to Aldosterone Excess and Raised Blood Pressure

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Abstract. Primary aldosteronism (PA) is a secondary hypertension characterized by autonomous aldosterone hypersecretion from adrenocortical adenoma and/or hyperplasia. Recently it has been suggested that aldosterone excess is directly involved in the development of cardiovascular injury in PA independent of its hypertensive effect. The present study was designed to examine the relationship between aldosterone excess and endothelial dysfunction in PA patients. 25 PA patients were studied for vascular endothelial function by ultrasound measurement of flow-mediated vasodilation (FMD), and 10 PA patients were re-evaluated 3 months after surgical or medical treatment; 10 age-, gender-, and blood pressure-matched hypertensive patients served as control subjects. Percent (%) FMD in PA patients (4.6±2.0%) was significantly (p < 0.0001) lower than that in the control subjects (7.9±2.0%). %FMD showed significant (p < 0.05) negative correlations with systolic blood pressure (SBP) (r=-0.48), brachial-ankle pulse wave velocity (r=-0.52), plasma aldosterone concentration (PAC) (r=-0.42), and aldosterone-renin ratio (ARR) (r=-0.42), while SBP showed a positive correlation with PAC (r=0.47). Percent FMD, SBP, PAC, and ARR significantly (p < 0.05) improved after surgical and medical treatment, although the changes of %FMD did not correlate with those of SBP, PAC or ARR. In conclusion, the present study has demonstrated that PA patients have endothelial dysfunction, which is related to aldosterone excess and raised blood pressure, and reversible after treatment, suggesting that aldosterone excess contributes to the development of endothelial dysfunction due to its hypertensive effect and/or its direct effect on the cardiovascular system.

Key words: Primary aldosteronism, Endothelial dysfunction, Flow-mediated vasodilation

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tion in healthy humans [10]. However, it remains unknown whether endothelial function is impaired in PA patients, and whether the correction of aldosterone excess could reverse endothelial dysfunction. To address these issues, the present study was designed to investigate the relationship of endothelial function to PAC and other clinical parameters in PA patients before and after correction of aldosterone excess by surgical and medical treatment.

**Subjects and Methods**

**Study population and patient characteristics**

This study was approved by the Ethics Committee of our institute, and written informed consent was provided from all subjects before enrollment. We studied 25 PA patients who consulted our clinics. They were treated with calcium channel blockers and/or α1-blockers during endocrinological examination. They were diagnosed as PA based on suppressed plasma renin activity (PRA) (≤ 1.0 ng/ml/h) and elevated PAC (≥ 12 ng/dl), greater PAC to PRA ratio (aldosterone-renin ratio: ARR) (≥ 20), and suppression of PRA (< 1.0 ng/ml/h) after stimulation with furosemide-upright. For localization of PA, adrenal CT and/or selective adrenal venous sampling (AVS) were performed in all 25 patients to differentiate between aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA). Ten age-, gender- and blood pressure-matched hypertensive control subjects were recruited and studied.

The clinical characteristics of PA patients and control subjects are shown in Table 1. Sixteen patients were diagnosed as APA and 9 patients as IHA by the localization studies. There were no significant differences of SBP and DBP between the two groups, since most of the PA patients (n=23) have received antihypertensives for blood pressure control. PAC, ARR, 24-h urinary aldosterone excretion, and baPWV in PA group were significantly (p < 0.05) higher, and PRA was lower than the control group. There were no significant differences of gender, age, smoking, lipid profile, hemoglobin A1c, fasting plasma glucose, serum potassium, and carotid IMT between the two groups.

Six APA patients had unilateral adrenalectomy and four IHA patients were treated with a mineralocorticoid receptor antagonist (spironolactone). Age, gender, blood pressure, PAC, PRA, ARR, and %FMD before treatment did not differ among the 25 patients.

**Measurements of hormonal and vascular functional parameters**

PRA and PAC were measured by radioimmunoassay kit using Renin-Riabead® (Dinabot, Tokyo, Japan) and SPAC-S Aldosterone® (TFB, Tokyo, Japan), respectively.

Flow-mediated vasodilation (FMD) of brachial artery was measured in all patients and control subjects using Sonos 5500 (Philips Medical Systems, Andover, MA, USA) as described [11]. Percent flow-mediated vasodilation (%FMD) and %nitroglycerin (NTG)-mediated vasodilation (%NMD) were expressed as the %increases in the maximal diameter from the baseline after cuff deflation within 120 sec, and 3 min after administration of NTG (0.3 mg), respectively. NTG was not administered in 9 PA patients because of their cardiovascular complications. Ten PA patients were re-evaluated for FMD and blood pressure 3 months after surgical or medical treatment.

Carotid artery intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) were measured as described previously [11] using ultrasound (Sonos 5500) and Form PWV/ABI (Omron Healthcare, Kyoto, Japan.), respectively.

**Statistical analysis**

Data are expressed as means ± standard deviation (SD) or median (interquartile range of 25-75%). A log transformation was performed for variables that did not follow a normal distribution. The χ² test was used for comparing proportions of subjects in the two groups. Comparison between groups was made using non-paired t test. Linear relationships between two continuous variables were tested by Pearson’s correlation coefficient. Difference of values between pre- and post-treatment in PA patients was analyzed using paired t test. All statistical analyses were performed using Windows software Prism 5.0 (GraphPad Software, La Jolla, CA, USA).

**Results**

As shown in Figure 1, %FMD in PA patients (4.6±2.0%) was significantly (p < 0.0001) lower than
Table 1. Clinical characteristics of patients with primary aldosteronism (PA) and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (APA / IHA)</strong></td>
<td>25 (16 / 9)</td>
<td>10</td>
</tr>
<tr>
<td><strong>Men / Women</strong></td>
<td>14 / 11</td>
<td>5 / 5</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>57.3±9.8</td>
<td>63.6±11.0</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>22.4±4.1</td>
<td>21.2±1.8</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>136±17</td>
<td>141±20</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>83±14</td>
<td>80±15</td>
</tr>
<tr>
<td><strong>Brachial-ankle pulse wave velocity (m/sec)</strong></td>
<td>17.0±2.1**</td>
<td>15.3±2.0</td>
</tr>
<tr>
<td><strong>Carotid intima-media thickness (mm)</strong></td>
<td>0.79±0.16</td>
<td>0.77±0.15</td>
</tr>
<tr>
<td><strong>Low-density lipoprotein cholesterol (mg/dL)</strong></td>
<td>107±27</td>
<td>121±21</td>
</tr>
<tr>
<td><strong>High-density lipoprotein cholesterol (mg/dL)</strong></td>
<td>60±20</td>
<td>57±23</td>
</tr>
<tr>
<td><strong>Triglyceride (mg/dL)</strong></td>
<td>107±56</td>
<td>115±39</td>
</tr>
<tr>
<td><strong>Fasting plasma glucose (mg/dL)</strong></td>
<td>5.4±0.5</td>
<td>5.4±0.6</td>
</tr>
<tr>
<td><strong>Insulin (μU/mL)</strong></td>
<td>101±25</td>
<td>101±14</td>
</tr>
<tr>
<td><strong>Fasting plasma glucose (mg/dL)</strong></td>
<td>5.0±3.8</td>
<td>3.7±1.9</td>
</tr>
<tr>
<td><strong>HOMA-R</strong></td>
<td>3.8±0.5</td>
<td>4.1±0.3</td>
</tr>
<tr>
<td><strong>Plasma aldosterone concentration (ng/dL)</strong></td>
<td>28.1±14.8*</td>
<td>10.5±6.4</td>
</tr>
<tr>
<td><strong>Plasma renin activity (ng/mL/h)</strong></td>
<td>0.3 [0.1-0.5]**</td>
<td>1.4 [0.3-2.9]</td>
</tr>
<tr>
<td><strong>Aldosterone-renin ratio (ARR)</strong></td>
<td>88 [46-253]***</td>
<td>9.5 [5.1-32.2]</td>
</tr>
<tr>
<td><strong>24-h urinary aldosterone excretion (μg/day)</strong></td>
<td>13.7±7.7*</td>
<td>7.9±4.8</td>
</tr>
</tbody>
</table>

APA: aldosterone-producing adenoma, IHA: idiopathic hyperaldosteronism, HOMA: Homeostasis model assessment insulin resistance index. Data means ± SD or median [interquartile range]. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. control group.

Fig. 1. Endothelium-dependent and -independent vasodilation in patients with primary aldosteronism (PA) and control subjects. (A) %FMD and (B) %NMD in (○) 10 control subjects and 25 PA patients (○: APA, ●: IHA). ***p < 0.0001.
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...decreased, and %FMD significantly (p < 0.05) increased after the treatment. However, the changes of %FMD did not show significant correlation with those of sbP, Pac, or arr.

Discussion

The present study has demonstrated for the first time that PA patients had endothelial dysfunction as assessed by FMD, which was significantly correlated with baPWV, Pac and arr as well as blood pressure, and reversible after treatment for PA.

To elucidate whether correction of aldosterone excess and/or action could reverse endothelial dysfunction, the changes of various hormonal and vascular parameters before and after surgical (n=6) or medical (n=4) treatment were examined in 10 PA patients. As shown in Figure 3, SBP, PAC, and ARR significantly (p < 0.05) decreased, and %FMD significantly (p < 0.05) increased after the treatment. However, the changes of %FMD did not show significant correlation with those of SBP, PAC, or ARR.
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independent of raised blood pressure. Our results are in accordance with those of a previous study showing that hypertensive patients with high PAC showed lower %FMD than those with normal PAC [9], although PA was not confirmed in these patients. Another study has also shown that patients with low renin-essential hypertension had impaired methacholine-induced vasodilation [22]. The negative correlations between %FMD and blood pressure, PAC and ARR in our PA patients suggest that endothelial dysfunction was attributable not only to hypertension, but also to aldosterone excess per se in PA patients.

The mechanism(s) by which aldosterone impairs endothelium-dependent vasodilation remains unknown. It has been shown that aldosterone directly inhibits NO production by decreasing endothelial NO synthase activity [23], and increases superoxide anion generation in endothelial cells [24]. Impaired endothelium-dependent vasodilation has been associated with enhanced degradation of NO by superoxide anion [25]. In addition, oxidative stress induced by aldosterone has been shown to be involved in the development of cardiovascular injury in aldosterone-induced hypertensive rats [26]. Thus, it is plausible to speculate that aldosterone-induced decrease in NO bioavailability and increase in ROS generation are involved in endothelial dysfunction in PA.

The improvement of %FMD after correction of aldosterone excess by surgical removal of adrenal tu-

![Fig. 3. Changes of vascular and hormonal parameters in PA patients before and after treatment.](image-url)
mor in APA or its action by receptor blockade in IHA by spironolactone as demonstrated in this study suggests that endothelial dysfunction associated with PA is reversible. Although we failed to observe significant correlations between the changes of %FMD and those of blood pressure, PAC and ARR, possibly due to small sample numbers, the present findings suggest that improvement in both raised blood pressure and aldosterone excess could equally contribute to the improvement of endothelial dysfunction.

The limitation of the present study is the relatively small number of PA patients and control subjects both in baseline and follow-up study, which prevented multivariate analysis from drawing a definite conclusion that aldosterone excess per se affects endothelial function independent of blood pressure. Further study using larger sample size of PA patients before and after treatment is required.

In conclusion, the present study has demonstrated that PA patients have endothelial dysfunction, which was related to aldosterone excess and raised blood pressure and reversible after treatment, suggesting that aldosterone excess contributes to the development of endothelial dysfunction due to its hypertensive effect and/or its direct effect on the cardiovascular system.

Acknowledgment

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