Involvement of Aldosterone in Left Ventricular Hypertrophy of Patients With End-Stage Renal Failure Treated With Hemodialysis

Atsuhisa Sato, John W. Funder, and Takao Saruta

There is increasing evidence about important cardiovascular effects of aldosterone through classic mineralocorticoid receptors in the heart. It is now clear that aldosterone/excess salt administration has been shown to produce both cardiac hypertrophy and interstitial cardiac fibrosis in rats. In clinical studies, it has been reported that aldosterone seems to play an important role in cardiac hypertrophy. However, it has still not been established whether aldosterone is involved in cardiac hypertrophy in patients with end-stage renal failure treated with hemodialysis. In the present study, we have analyzed the association between cardiac hypertrophy and aldosterone in 29 patients (18 patients with nondiabetic nephropathy and 11 patients with diabetic nephropathy) who developed end-stage renal disease and received hemodialysis. Among the nondiabetic patients, left ventricular mass index correlated significantly with plasma aldosterone concentrations during both before and after hemodialysis, but it did not correlate with plasma renin activity. Furthermore, left ventricular mass index also correlated with mean blood pressure. In contrast, these correlations were not seen in the diabetic patients, despite similar age distribution, duration of hemodialysis, and several echocardiographic parameters between two groups. In conclusion, our study provides new evidence for a relation between left ventricular hypertrophy and plasma aldosterone concentrations that seems to be independent of blood pressure in nondiabetic patients with end-stage renal failure treated with hemodialysis.


KEY WORDS: Aldosterone, mineralocorticoid receptor, cardiac hypertrophy, diabetes.

Classically, the primary roles of aldosterone in circulatory homeostasis and salt/water balance have been thought to be mediated by way of epithelial mineralocorticoid receptors (MR). In epithelial target tissues it is now clear that the specificity of aldosterone action is enzyme, rather than receptor, mediated. More recently, there is increasing evidence for important cardiovascular effects of aldosterone via classic MR in nonepithelial tissues such as brain and heart. In the heart, MR has been demonstrated by aldosterone-binding studies, both in vivo and in vitro, and the
mRNA for MR has been located by Northern blot analysis. Recently, we and other investigators have demonstrated that aldosterone/excess salt administration has been shown to produce both cardiac hypertrophy and interstitial and perivascular cardiac fibrosis in rats, independent of blood pressure (BP), and at least in the case of collagen deposition, very probably reflecting a direct effect of aldosterone on the heart mediated by cardiac MR.

In clinical studies, it has been reported that aldosterone seems to play an important role in cardiac hypertrophy in moderate essential hypertensive patients, independent of its relationship with BP. Moreover, left ventricular (LV) hypertrophy has been shown to be more prominent in patients with primary aldosteronism than in patients with other types of secondary hypertension, and a positive correlation was found between LV mass index (LVMl) and plasma aldosterone concentrations in these patients. Finally, LV hypertrophy has been shown to precede other target organ damage in patients with primary aldosteronism. Taken together with the results of these clinical and experimental studies, it is very likely that aldosterone is primarily involved in the regulation of cardiac hypertrophy through nonepithelial cardiac MR.

The renin-angiotensin system has been reported to play an important role in maintaining BP in patients with end-stage renal failure treated with hemodialysis. However, it has not been established whether aldosterone is involved in cardiac hypertrophy in these patients. Therefore, the present study explores the potential physiologic and pathologic roles for aldosterone in terms of cardiac hypertrophy in patients with end-stage renal failure treated with hemodialysis. We have analyzed the association between cardiac hypertrophy and aldosterone in 29 patients who developed end-stage renal disease and received hemodialysis in our institution. Because most patients treated with hemodialysis in our institution are hypertensive and receive antihypertensive treatment, we have also analyzed involvement of hypertension and antihypertensive treatment in cardiac hypertrophy in these patients. Previously, we have reported that patients with diabetic nephropathy show an altered response in terms of plasma renin activity and aldosterone to hemodialysis, compared to nondiabetic patients. In the present study, therefore, we analyzed the data from patients with diabetic nephropathy and nondiabetic patients, respectively.

MATERIALS AND METHODS

Patients Twenty-nine patients who have received hemodialysis treatment for more than 1 year for end-stage renal failure seen at Mito Red Cross Hospital, Ibaraki, Japan, participated in this study. Eighteen patients had nondiabetic nephropathy (chronic glomerulonephritis) (12 men, 6 women; mean age, 52 ± 17 years), and 11 patients had diabetic nephropathy (8 men, 3 women; mean age, 60 ± 11 years). All patients were hypertensive and were receiving antihypertensive treatment. Of the 11 patients with diabetic nephropathy, 8 patients were treated with insulin and 3 patients by dietary therapy. BP was measured with a mercury sphygmomanometer after at least 10 min of rest in the supine position, and expressed as the mean of three consecutive measurements as described previously. The mean BP (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. The heart rate was obtained from the radial pulse over 30 sec. Hypertension was defined as a systolic BP of more than 160 mm Hg or a diastolic BP of more than 95 mm Hg.

Neurohumoral Factors Prehemodialysis blood samples were taken at 9:00 AM on the day of the echocardiographic examination after the patients had been lying supine for at least 10 min. Hemodialysis was performed using a dialysate containing Na⁺ 140 mEq/L, K⁺ 2.0 mEq/L, Cl⁻ 110 mEq/L, Ca²⁺ 3.0 mEq/L, Mg²⁺ 1.0 mEq/L, and blood samples were collected after hemodialysis. Plasma renin activity was measured with a commercial radioimmunoassay from plasma renin activity SRL (Dai-ichi Radio-isotope, Tokyo, Japan), and aldosterone with a commercial radioimmunoassay from SPAC-S Aldosterone Kit (Dai-ichi Radio-isotope, Tokyo, Japan). Plasma renin activity was determined by measuring newly synthesized angiotensin I with an angiotensinase inhibitor and PMSF. Our preliminary study showed that angiotensin I is not synthesized at 4°C, which suggests that renin activity is completely repressed at this temperature. Therefore, we did not subtract the value at 4°C from that at 37°C, because the value at 4°C is almost zero. After drawing blood, we put it on ice and centrifuged it at 4°C. In our preliminary study plasma renin activity was determined by two different assay procedures. The first was intended to determine plasma renin activity immediately after collecting samples, and the other was to determine plasma renin activity in the same sample after it was placed on ice for 30 min. Almost identical results were found: 2.79 ± 0.45 ng/mL/h in the first method, and 2.79 ± 0.46 ng/mL/h in the second method (n = 20). Correlation between the two methods was r = 0.997. These results suggest that the method used in this study did not affect the value of plasma renin activity when compared with method that does not use ice. The normal range of plasma renin activity in the supine position in our assay was 0.3 to 2.9 ng/mL/h, and our assay sensitivity was 0.1 to 20 ng/mL/h. In this study, according to previous studies suggesting that aldosterone plays an important role in the genesis of cardiac hypertrophy, we...
used the value of plasma renin activity in the supine position, not the seated position in which the plasma renin activity may be higher.

Echocardiography and Patterns of LV Geometry

Echocardiographic studies were performed by standard methods with SSA-380A echocardiography with a 5.0-MHz transducer (Toshiba, Japan), according to the recommendations of the American Society of Echocardiography. LV mass was estimated from the following formula of Devereux and Reichek (Penn convention): LV mass (g) = 1.04 × [(LVDD + IVST + PWT)3 − (LVDD)3] − 13.6, where LVDD is LV end-diastolic dimension, IVST is interventricular septal thickness, and PWT is posterior wall thickness. The LVMI was calculated for each patient by dividing the LV mass by the body surface area. Relative wall thickness was measured at end-diastole as twice (PWT/LVDD). Recent studies have shown that LV thickening can occur without an abnormal increase in overall LV muscle mass; patients with increased LVMI and normal relative wall thickness were considered to have eccentric LV remodeling.

Statistical Analysis

Data are expressed as mean ± SD, and statistical significance between two groups determined by two-tailed, unpaired t test (Mann-Whitney). Changes in parameters during hemodialysis in each group were compared by two-group paired t test (Wilcoxon signed-rank test), with P < .05 taken as significant. Univariate correlation was established by Pearson’s correlation coefficient.

RESULTS

Clinical and Echocardiographic Data

The clinical and echocardiographic studies are summarized in Table 1. In clinical terms, there were no significant differences in age or duration of hemodialysis between nondiabetic patients and diabetic patients. In terms of the echocardiographic data, there were also no significant differences in LVMI, relative wall thickness, or other major echocardiographic parameters between the two groups. However, values for the LVMI of both nondiabetic (186 ± 61 g/m²) and diabetic patients (181 ± 44 g/m²) in this study were much higher than those reported in other studies exploring the influence of BP on LV hypertrophy in hypertensive patients.

Patterns of LV Geometry

As shown in Figure 1, in both groups nearly half of the patients showed concentric LV hypertrophy. Furthermore, there were no patients with a normal left ventricle among the diabetic patients.

Changes in Plasma Renin Activity, Aldosterone, and MAP During Hemodialysis in Diabetic and Nondiabetic Patients

Table 2 shows the changes in systolic and diastolic BP, plasma renin activity, plasma aldosterone concentration, and serum potassium levels. During hemodialysis, BP in both groups of patients decreased to a similar extent. No significant changes in plasma renin activity during hemodialysis were ob-

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**TABLE 1. CLINICAL AND ECHOCARDIOGRAPHIC DATA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-DM (n = 18)</th>
<th>DM (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>12/6</td>
<td>8/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 17</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Duration of HD (months)</td>
<td>31 ± 18</td>
<td>26 ± 13</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-HD</td>
<td>106 ± 12</td>
<td>107 ± 6</td>
</tr>
<tr>
<td>post-HD</td>
<td>99 ± 10</td>
<td>97 ± 10</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>186 ± 61</td>
<td>181 ± 44</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.51 ± 0.19</td>
<td>0.48 ± 0.13</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>50 ± 9</td>
<td>51 ± 9</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>12 ± 3</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>12 ± 3</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.5 ± 1.1</td>
<td>3.7 ± 1.9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.64 ± 0.12</td>
<td>0.64 ± 0.13</td>
</tr>
</tbody>
</table>

All values are mean ± SD. DM, diabetes mellitus; HD, hemodialysis; MAP, mean arterial pressure; LVMI, left ventricular mass index; LVDD, left ventricular end-diastolic dimension; IVST, interventricular septal thickness; PWT, posterior wall thickness; CI, cardiac index; EF, ejection fraction.

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**FIGURE 1.** Classification of left ventricular hypertrophy (LVH) according to left ventricular geometric pattern. Open bars show nondiabetic group, and hatched bars the diabetic group. Normal, normal left ventricle; LVR, concentric left ventricular remodeling.
served in either group. However, a significant decrease in aldosterone during hemodialysis was seen in the nondiabetic patients. In contrast, no significant changes in aldosterone were seen in the diabetic patients, although the changes in serum potassium were not significantly different between the two groups. Moreover, the baseline values of plasma aldosterone concentrations were lower in the diabetic group than those in the nondiabetics, although the results did not reach statistical significance. These aldosterone values, both at baseline and during hemodialysis, are consistent with the results of our previous study.15 We performed computed tomographic scan and echo studies on the three nondiabetic patients with prehemodialysis aldosterone values more than 500 pg/mL, with no patients showing evidence for adrenal tumor or hyperplasia.

### Aldosterone Plays an Important Role in Cardiac Hypertrophy in Nondiabetic Patients With End-Stage Renal Failure Treated With Hemodialysis

In the nondiabetic group, LVMI correlated significantly with plasma aldosterone concentration both before \((r = 0.509, P = .03)\) and after hemodialysis \((r = 0.492, P = .04)\) (Figure 2), but not with plasma renin activity. In nondiabetic patients LVMI also correlated with MAP (before, \(r = 0.494, P = .04\); after hemodialysis, \(r = 0.582, P = .01\)); neither plasma renin activity nor plasma aldosterone concentrations correlated with MAP in these patients. Plasma renin activity and serum potassium are the major determinants of aldosterone synthesis. In relation to the water balance during hemodialysis, plasma renin activity should increase after hemodialysis, but in this study plasma renin activity did not change during hemodialysis. These results strongly suggest that patients who have received hemodialysis treatment for more than 1 year for end-stage renal failure may not maintain their renal function in terms of renin secretion. Therefore, it is quite conceivable that the relationship between plasma renin activity and the aldosterone level may be obscured.

In contrast, there were no correlations between LVMI and plasma aldosterone concentrations (before, \(r = 0.165, P = .629\); after hemodialysis, \(r = 0.333, P = .318\), plasma renin activity (before, \(r = 0.370, P = .262\); after hemodialysis, \(r = 0.388, P = .213\), or MAP (before, \(r = 0.06, P = .86\); after hemodialysis, \(r = 0.198, P = .56\) in the diabetic group. In both groups, there was no significant correlation between LVMI and aldosterone before hemodialysis \((r = 0.419, P = .02)\), and LVMI and MAP (before, \(r = 0.393, P = .04\);

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**TABLE 2. CHANGES IN SYSTOLIC BP, DIASTOLIC BP, PLASMA RENIN ACTIVITY (PRA), ALDOSTERONE (ALDO), AND SERUM POTASSIUM (K) DURING HEMODIALYSIS (HD) IN NONDIABETIC (NON-DM) AND DIABETIC (DM) PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>Non-DM (n = 18)</th>
<th>DM (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td></td>
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</tr>
<tr>
<td>Pre-HD</td>
<td>153 ± 14</td>
<td>155 ± 10</td>
</tr>
<tr>
<td>Post-HD</td>
<td>142 ± 14*</td>
<td>141 ± 14*</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD</td>
<td>83 ± 13</td>
<td>81 ± 15</td>
</tr>
<tr>
<td>Post-HD</td>
<td>78 ± 11*</td>
<td>76 ± 11*</td>
</tr>
<tr>
<td><strong>PRA (ng/mL/h)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD</td>
<td>3.5 ± 4.2</td>
<td>2.2 ± 3.1</td>
</tr>
<tr>
<td>Post-HD</td>
<td>3.5 ± 4.8</td>
<td>2.4 ± 3.1</td>
</tr>
<tr>
<td><strong>ALDO (pg/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD</td>
<td>249 ± 241</td>
<td>101 ± 39</td>
</tr>
<tr>
<td>Post-HD</td>
<td>181 ± 180*</td>
<td>128 ± 72</td>
</tr>
<tr>
<td><strong>K (mEq/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD</td>
<td>5.5 ± 0.8</td>
<td>5.3 ± 0.9</td>
</tr>
<tr>
<td>Post-HD</td>
<td>3.9 ± 0.4*</td>
<td>3.9 ± 0.6*</td>
</tr>
</tbody>
</table>

*All values are mean ± SD.* $^*P < .05$ v prehemodialysis value.

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**FIGURE 2.** Relationship between left ventricular mass index (LVMI) and plasma aldosterone concentrations (Aldeosterone) before (A) and after hemodialysis (B) in nondiabetic patients treated with hemodialysis.
after hemodialysis, \( r = 0.418, \ P = .03 \) were preserved. Finally, we have analyzed the effects of various forms of antihypertensive treatment on LVMI, MAP, plasma renin activity, and plasma aldosterone concentration in nondiabetic patients. Except for one patient who received \( \alpha_1 \)-blocker alone, patients received either a calcium channel blocker alone (eight patients) or a calcium channel blocker plus other drugs (seven patients; calcium channel blocker plus \( \alpha_1 \)-blocker, one patient; calcium channel blocker plus \( \alpha_1 \beta \)-blocker, one patient; calcium channel blocker plus \( \alpha_1 \)-blocker and angiotensin converting enzyme inhibitor). Therefore, we have compared the data from patients treated with calcium channel blocker alone and findings from patients with calcium channel blocker plus other drugs and found no significant difference in LVMI, MAP, plasma renin activity, or plasma aldosterone concentration. Only one nondiabetic patient received an angiotensin converting enzyme inhibitor with the other two antihypertensive drugs. His plasma renin activity was 3.0 ng/mL/h before hemodialysis, 2.7 ng/mL/h after hemodialysis, and plasma aldosterone concentration was 330 pg/mL before hemodialysis, 270 pg/mL after hemodialysis. We know that the angiotensin converting enzyme inhibitor may dissociate the levels of plasma renin activity from aldosterone, but essentially identical results were obtained except for his data.

**DISCUSSION**

This is the first report to suggest that aldosterone may play an important role in cardiac hypertrophy in the patients with end-stage renal failure treated with hemodialysis. Moreover, the findings in the present study are also of interest from another point of view, suggesting the possibility of different mechanisms of cardiac hypertrophy between patients with nondiabetic nephropathy and those with diabetic nephropathy.

MR have been demonstrated in cytosol preparations of all four chambers of the heart.\(^5\) In the adrenalecto-
mized rat in vivo, cardiac MR (like those in the hippocampus) bind aldosterone and corticosterone with equal affinity, in contrast with classic aldosterone target tissues such as kidney and colon.\(^4\) This is consistent with the absence from heart and hippocampus of 11\( \beta \)-hydroxysteroid dehydrogenase type 2 (11\( \beta \)-HSD2),\(^{25} \) the low \( K_m \), NAD-requiring, operationally unidirectional dehydrogenase that protects MR in aldosterone target tissues by local conversion of cortisol/corticosterone into their receptor-inactive 11-keto metabolites. Given the much higher plasma-free levels of glucocorticoids, cardiac MR in vivo are presumably overwhelmingly occupied by glucocorticoids.

Recently, we have demonstrated that occupancy by aldosterone of such unprotected, “always occupied” MR causes cardiac fibrosis and hypertrophy in rats,\(^7,^8\) and have explored the role of aldosterone and salt in cardiac fibrosis. First, the hypertrophic effect is mineralocorticoid specific, in that it is seen with aldosterone and deoxycorticosterone, but not with high doses of corticosterone.\(^6\) Second, an aldosterone–salt imbalance appears essential for cardiac hypertrophy, in that aldosterone-infused rats maintained on a low salt diet have normal heart-to-body weight ratios.\(^7\) Third, the hypertrophy is not a structural response to the hemodynamic demands of elevated BP, in that rats infused peripherally with aldosterone and intracerebroventricularly with the synthetic spironolactone analog RU 28318 are normotensive, but have levels of cardiac hypertrophy identical to those in animals infused with aldosterone alone.\(^7\)

In the present study, we have explored the possible role of aldosterone in cardiac hypertrophy in patients with end-stage renal failure treated with hemodialysis. The most important finding of the present study is the correlation of plasma aldosterone concentration with LVMI in nondiabetic patients treated with hemodialysis. As recognition of the risk associated with LV hypertrophy has grown, there is increasing evidence that reduction of ventricular mass is a desirable goal of antihypertensive treatment. For patients with moderate hypertension, LV mass reduction and normalization of LV geometry have been reported to strongly suggest a favorable prognosis in these patients.\(^{22-27} \)

If similar prognostic considerations apply for hemodialysis patients, the present study may serve to flag a question of potential clinical relevance, that of an important role for aldosterone in the genesis of cardiac hypertrophy in these patients. Taken together with the results that there was no correlation between LVMI and duration of hemodialysis, nor with age, and that MAP correlated with neither plasma renin activity nor aldosterone levels, it suggests that the routine measurement and vigorous control of aldosterone levels, as well as of BP, may be important for the prevention of cardiac hypertrophy in nondiabetic patients treated by hemodialysis. Previously, we have shown that aldosterone and excess salt produce cardiac hypertrophy, independent of BP,\(^7,^8\) and we tried to extend these studies in this clinical study. However, the majority of patients who have received hemodialysis treatment for more than 1 year in our hospital are hypertensive. Therefore, unfortunately we could not obtain sufficient data from normotensive subjects in this study.

In diabetic patients, neither plasma levels of aldosterone, which are lower than those of nondiabetic patients, nor MAP was found to correlate with LVMI. However, we have shown previously that high glucose levels stimulate aldosterone-induced hypertrophy in rat cardiomyocytes,\(^28\) which suggests that
lower levels of aldosterone may cause cardiac hypertrophy under high glucose conditions. Considering the altered response of plasma renin activity and aldosterone to hemodialysis in diabetic patients in previous\textsuperscript{15} and the present study, pathophysiologic roles for aldosterone on the heart under high glucose conditions may be more complicated in vivo, and will require further studies, both in basic and clinical. Furthermore, given that no diabetic patient showed normal LV geometry, and that our echocardiographic study showed LVMI much higher than that reported in other studies, it would appear that patients apparently stable on hemodialysis may be particularly vulnerable in terms of cardiac hypertrophy.

Finally, our data were obtained in a small sample size; therefore, our study has several limitations. Our conclusion cannot be assumed to apply to patients on hemodialysis treatment for less than 1 year, and with other causes of end-stage renal failure. We also could not analyze accurately the difference for each antihypertensive treatment because of the small sample size. We believe that a larger study would help confirm our findings. However, our study provides new evidence for a relation between cardiac hypertrophy and plasma aldosterone concentrations in hemodialysis patients. Given that a cardiovascular event is a major cause of death in patients treated with hemodialysis, the present study may serve to pose a question of potential clinical relevance, namely, does aldosterone play an important role in the genesis of cardiac hypertrophy in these patients.

In conclusion, in nondiabetic patients with end-stage renal failure treated with hemodialysis our study provides new evidence for a relation between LV hypertrophy and plasma aldosterone concentrations in hemodialysis patients, which appears independent of arterial BP. Further studies on pathophysiologic roles of aldosterone in patients treated with hemodialysis will be needed to establish the possibility of direct involvement of aldosterone in cardiac hypertrophy in these patients.

**ACKNOWLEDGMENTS**

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**REFERENCES**


19. Devereux RB, Reichek N: Echocardiographic determi-


21. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–352.


