Echocardiographic Comparison of Left Ventricular Structure and Function in Hypertensive Patients With Primary Aldosteronism and Essential Hypertension

Ronen Goldkorn, Alexei Yurenev, Jon Blumenfeld, Dawn Fishman, and Richard B. Devereux

Background: In experimental renovascular hypertension, aldosterone has been implicated in myocardial remodeling and fibrosis, but it is uncertain whether excess aldosterone affects left ventricular structure and function in hypertensive patients.

Methods: Hypertensive patients from the Cardiovascular Center of the New York Presbyterian Hospital-Weill Cornell Medical Center in New York and the Russian Cardiovascular Research Institute, Moscow, Russia, were studied. The sample included 35 patients with primary aldosteronism and 35 controls with essential hypertension matched for age, gender, and blood pressure (BP). Left ventricular (LV) mass, endocardial and midwall fractional shortening, and circumferential end-systolic stress were calculated. The observed/predicted midwall shortening ratio was used as an index of LV performance corrected for afterload.

Results: Primary aldosteronism and essential hypertension patients had comparable LV dimensions, wall thickness, mass, mass/body surface area, and mass/height. Endocardial and midwall fractional shortening, and afterload-corrected midwall shortening were similar in primary aldosteronism and essential hypertension groups from both clinics. Moreover, logistic regression analysis using BP, body mass index, height, gender, and center as covariates failed to identify statistical differences in LV geometry or systolic function between primary aldosteronism and essential hypertension patients.

Conclusions: Patients with primary aldosteronism, a state characterized by chronic aldosterone excess, had similar LV geometry and systolic function compared to essential hypertension patients matched for age, gender, and BP. This argues against important independent associations between aldosterone and these aspects of LV response to human hypertension. Am J Hypertens 2002;15:340–345 © 2002 American Journal of Hypertension, Ltd.

Key Words: Aldosterone, echocardiography, hypertension, left ventricle.

The most serious target organ manifestation of hypertension is left ventricular hypertrophy (LVH). Left ventricular (LV) remodeling can lead to deterioration in systolic and diastolic function and LVH may predict an adverse prognosis more strongly than any cardiovascular risk factor except for age. It is now known that the LV may undergo several distinct geometric adaptations, including concentric hypertrophy, eccentric hypertrophy, and concentric remodeling. Moreover, the level of cardiovascular risk differs among these geometric patterns.

The heterogeneity of LV geometric adaptations to hypertension may be influenced by differential contributions of various circulating hormones in different subsets of hypertension. The renin-angiotensin-aldosterone system reportedly plays an independent role in the pathogenesis of LVH. In a rat model of renovascular hypertension, in which renal ischemia leads to activation of the renin-angiotensin-aldosterone system, cardiac myocyte necrosis is followed by fibroblast proliferation and myocardial remodeling. These events can be prevented by administration of the angiotensin converting enzyme inhibitor captopril.
Aldosterone may cause extracellular matrix and collagen deposition and therefore stimulate myocardial fibrosis. However, it is unclear whether excess aldosterone in human patients plays a pathogenic role in LV geometric and contractile abnormalities beyond those expected for elevated blood pressure (BP) alone.

Primary aldosteronism (PA) is a condition that offers the unique opportunity to examine this question. The LV geometry and function have been examined in several series of patients with PA by echocardiography. One study reported that concentric LVH and concentric remodeling were more prevalent in patients with PA. However, available studies have been relatively small ones of subjects from single centers and have not assessed LV myocardial contractility using recently derived indices, such as the midwall fractional shortening/circumferential end-systolic stress relation. This methodology accurately identifies hypertensive patients with depressed LV myocardial function, and predicts cardiovascular risk independently of age, BP, or LV mass.

In this two-center, case-control study we compared LV geometry and function between patients with PA and essential hypertension matched for relevant variables including age, gender, and BP.

Methods

Subjects

The study group was comprised of hypertensive patients evaluated at the Cardiovascular Center of New York Presbyterian Hospital-Weill Cornell Medical Center in New York City and the Russian Cardiovascular Research Institute, Moscow, Russia. Thirty-five patients with PA (19 from New York, 16 from Moscow), and equal numbers of essential hypertensive patients from each center were matched for age, gender, and BP. The diagnosis of primary aldosteronism was established by the following criteria: 1) hypertension; 2) either elevated urinary aldosterone excretion as determined by an established nomogram that relates 24-h urinary sodium excretion to urinary aldosterone and plasma renin activity (in NY patients) or elevated plasma levels of aldosterone (in Moscow patients); 3) low plasma renin activity when its level could be determined off medications known to stimulate renin release; and 4) hypokalemia that was either spontaneous or diuretic induced and associated with inappropriate renal potassium loss (>40 mmol/d). Patients with primary aldosteronism included 7 New York and 12 Moscow patients diagnosed with a nonmalignant adenoma and 12 New York and 4 Moscow patients with bilateral adrenal hyperplasia.

Laboratory Tests

Assays for plasma renin activity and urinary aldosterone, as well as the overall approach to patient evaluation, have been described previously. Serum electrolyte and creatinine concentrations and 24-h urinary sodium and potassium were measured by standard analytical technique.

Echocardiography

M-mode echocardiograms were recorded with commercially available echocardiographs and 2.25-MHz transducers, in a dimly lit room, with the patients in partial left decubitus position. Procedures for visualization and interpretation of LV structures were previously described. The LV mass was calculated by the Penn convention recommendations. The LV measurements were made in New York and Moscow by two experienced investigators who had jointly read echocardiograms in previous studies.

To take into account the different relations between body size and three-dimensional volumes (such as that of the myocardium) or one-dimensional linear measurements, LV chamber dimension was indexed for the first power of height, whereas LV mass was normalized for height to the 2.7 power on the basis of results of a multicenter study.

To measure LV systolic function, measurements of septal and posterior wall thickness and LV chamber dimensions were obtained according to the American Society of Echocardiography recommendations. Standard methods were used to calculate endocardial fractional shortening. Circumferential end-systolic stress (cESS) was calculated at the midwall at the level of the LV minor axis by the method of GaaSchie et al as the primary measure of myocardial afterload. Calculation of midwall fractional shortening took into account the epicardial migration of the midwall during systole by using a modified ellipsoidal model similar to that used to calculate LV mass. An equation relating midwall shortening to circumferential end-systolic stress in 142 normal subjects was used to predict expected midwall shortening for observed end-systolic stress in this hypertensive population. The ratio of observed-to-predicted midwall shortening was termed stress-corrected midwall shortening, and used as an index of LV contractile performance.

Statistics

Data are expressed as mean value ± SD. Two-way ANOVA using center of origin as a covariate along with the main comparison between PA and essential hypertension (EH) patients was performed to determine significant associations of clinical and echocardiographic variables. Multiple linear regressions were performed using BP, body mass index (BMI), height, gender, center, and indicator variables for medication classes as covariates to test associations of an indicator variable for PA versus EH with LV structural and functional variables. In all analyses, two-tailed P < .05 indicated statistical significance.
LV mass/BSA (g/m²) 113.6
LV mass (g) 216.3
ESV (mL) 54.4

LV mass/height².7 47.9
PWTd (cm) 0.98
IVSd (cm) 1.1

Left ventricular geometric characteristics in patients with primary aldosteronism and essential hypertension

|                  | New York         | Essential Hypertension | Moscow          | Essential Hypertension | ANOVA
|------------------|-------------------|------------------------|-------------------|------------------------|-------
| Primary Aldosteronism | (n = 19)          | (n = 19)               | (n = 16)         | (n = 16)               | Group P | Center P |
| Age (y)          | 49.6 ± 7.3        | 48.8 ± 6.9             | 49.3 ± 6.9       | 48.3 ± 6.9             | .80    | .21      |
| Systolic BP (mm Hg) | 167.8 ± 25.2      | 166.4 ± 22.2           | 191.9 ± 29.3     | 194.1 ± 36.1           | .73    | .003     |
| Diastolic BP (mm Hg) | 101.6 ± 14.4      | 103.4 ± 13.4           | 116.3 ± 15.0     | 117.2 ± 18.1           | .59    | .002     |
| Mean BP (mm Hg)  | 123.5 ± 16.0      | 124.2 ± 15.0           | 141.5 ± 19.0     | 142.8 ± 21.1           | .62    | .001     |
| Height (cm)      | 72.2 ± 9.7        | 72.3 ± 10.0            | 69.2 ± 7.4       | 69.4 ± 9.9             | .62    | .27      |
| Weight (kg)      | 73.1 ± 17.8       | 68.1 ± 12.3            | 76.8 ± 11.4      | 83.1 ± 8.1             | .97    | .005     |
| BSA (m²)         | 1.86 ± .26        | 1.79 ± .19             | 1.83 ± .13       | 1.94 ± .13             | .79    | .17      |
| BMI (kg/m²)      | 24.2 ± 3.7        | 23.4 ± 2.9             | 28.5 ± 4.9       | 27.6 ± 2.2             | .60    | .000     |
| PRA (ng/mL/h)    | 0.53 ± .48        | 1.9 ± 2.3              | 0.51 ± .97       | 1.0 ± 1.4              | .03    | .12      |
| Urinary aldosterone (µg/day) | 41.5 ± 45.2 | 10.9 ± 10.6 | N/A | N/A | N/A | N/A | N/A |
| Plasma aldosterone (pmol/L) | N/A | N/A | 626.6 ± 106.9 | 109.3 ± 20.0 | N/A | N/A | N/A |

Table 1. Characteristics of patients with primary aldosteronism and essential hypertension from New York and Moscow

Results

Table 1 shows the characteristics of study patients from New York and Moscow. The PA patients were well matched with EH patients for age, BP, and heart rate in both centers. The PA patients from Moscow were slightly smaller than their EH counterparts, with lower height and body surface area (BSA) values. Plasma renin activity (PRA) values were lower in PA patients. By definition, urinary aldosterone (New York patients) and plasma aldosterone (Russian patients) levels were higher in PA patients. At the time of study, 14 PA and 2 EH patients in New York and 12 PA and 9 EH patients in Moscow were medicated.

Tables 2 and 3 compare echocardiographic variables between PA patients and EH controls. The LV internal dimensions and wall thickness (including end-diastolic relative wall thickness) were similar in the PA and EH patients. Moreover, LV mass, mass/BSA, and mass/height².7 were comparable in PA and EH patients from both centers. Systolic function, measured as fractional shortening at the endocardial surface as well as midwall shortening, was statistically similar for the patient groups.
Most important, stress-corrected midwall shortening, an index of LV performance that is adjusted for myocardial afterload, was not significantly different between the PA and EH groups from either New York or Moscow (Table 3). Finally, Table 4 demonstrates that several cardiac and peripheral hemodynamic parameters were also comparable for the two patient groups from both clinical centers.

To account for the variance introduced by the center of origin (New York or Moscow), two-way analyses of variance (ANOVA) were carried out comparing the PA patients to their matched controls with respect to all the variables included in Tables 2 to 4. The various indices of LV mass or of the parameters of systolic function or systemic hemodynamics were identified by multivariate analyses. Alternative regression analyses using urine or plasma aldosterone as continuous variables did not identify independent associations with LV mass or stress-corrected midwall shortening ($P = .09$ to .82).

### Discussion

In this two-center, case-control study we used echocardiography to compare LV geometry and function in hypertensive patients with PA to equally hypertensive patients with EH. The sample included patients from clinical centers in New York and Moscow, matched for age, gender, and BP. We assessed LV structure by examining LV dimensions, LV mass, and various LV mass indices, including LV mass/height$^3$-$^7$, a method of indexation shown to reflect the normal heart to body size relation. $^{30,36}$ The LV systolic function was studied conventionally at the

#### Table 3. Left ventricular functional characteristics in patients with primary aldosteronism and essential hypertension

<table>
<thead>
<tr>
<th></th>
<th>New York</th>
<th>Moscow</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Aldosteronism (n = 19)</td>
<td>Essential Hypertension (n = 19)</td>
<td>Primary Aldosteronism (n = 16)</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>83.8 ± 29.5</td>
<td>77.6 ± 24.0</td>
<td>87.1 ± 22.3</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.62 ± 0.07</td>
<td>0.65 ± 0.09</td>
<td>0.69 ± 0.08</td>
</tr>
<tr>
<td>cESS (kdyne/cm$^2$)</td>
<td>175.8 ± 53.8</td>
<td>161.5 ± 74.8</td>
<td>177.9 ± 53.1</td>
</tr>
<tr>
<td>eFS (%)</td>
<td>0.34 ± 0.05</td>
<td>0.36 ± 0.06</td>
<td>0.39 ± 0.06</td>
</tr>
<tr>
<td>MWS (%)</td>
<td>0.17 ± 0.03</td>
<td>0.16 ± 0.03</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>Stress-corrected MWS (%)</td>
<td>103.0 ± 20.3</td>
<td>99.7 ± 24.7</td>
<td>102.6 ± 11.2</td>
</tr>
</tbody>
</table>

Group = aldosteronism v essential hypertension; Center = New York v Moscow; SV = stroke volume; EF = ejection fraction; cESS = circumferential end-systolic stress; eFS = endocardial fractional shortening; MWS = midwall shortening.

#### Table 4. Systemic hemodynamics in patients with primary aldosteronism and essential hypertension

<table>
<thead>
<tr>
<th></th>
<th>New York</th>
<th>Moscow</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Aldosteronism (n = 19)</td>
<td>Essential Hypertension (n = 16)</td>
<td>Primary Aldosteronism (n = 16)</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.1 ± 2.4</td>
<td>5.6 ± 1.9</td>
<td>6.0 ± 1.5</td>
</tr>
<tr>
<td>Cardiac index (L/min/m$^2$)</td>
<td>3.2 ± 1.1</td>
<td>3.1 ± .9</td>
<td>3.3 ± .7</td>
</tr>
<tr>
<td>TPR (dynes $\cdot$ s $\cdot$ cm$^{-5} \cdot$ m$^2$)</td>
<td>1822 ± 603</td>
<td>1971 ± 683</td>
<td>1992 ± 542</td>
</tr>
<tr>
<td>TPR $\times$ BSA (dynes $\cdot$ s $\cdot$ cm$^{-5}$)</td>
<td>3312 ± 983</td>
<td>3484 ± 1189</td>
<td>3608 ± 838</td>
</tr>
<tr>
<td>PP/SV (mm Hg/mL)</td>
<td>0.88 ± .39</td>
<td>0.86 ± .26</td>
<td>0.91 ± .28</td>
</tr>
<tr>
<td>PP/SI (mm Hg/mL$^2$)</td>
<td>1.57 ± .60</td>
<td>1.53 ± .47</td>
<td>1.66 ± .50</td>
</tr>
</tbody>
</table>

Group = aldosteronism v essential hypertension; Center = New York v Moscow; TPR = total peripheral resistance; TPR $\times$ BSA = total peripheral resistance indexed for body surface area; PP/SV = pulse pressure/stroke volume; PP/SI = pulse pressure/stroke index.
endocardial surface, as well as by using the midwall fractional shortening circumferential end-systolic stress relation, a method that more accurately identifies hypertensive patients with decreased LV function, and strongly predicts cardiovascular risk.

The principal finding was that there were no significant elevations in LV internal dimensions or wall thickness in the PA compared to the EH groups; in fact, the only significant intergroup difference was a slightly higher LV relative wall thickness in EH than in PA patients. As a result, there were no intergroup differences in LV mass indices or any of the parameters reflecting LV systolic function. Moreover, stress-corrected LV midwall shortening, an index of LV myocardial contractility, was not statistically different between the PA and EH groups in either New York or Moscow.

The present results contrast with those of several previous studies. Janota et al found slightly increased LV posterior wall thickness, whereas Denolle et al found increased LV posterior wall thickness, septal thickness, and LV mass/BSA in 21 patients with aldosterone-producing adenoma compared with 52 patients with other forms of secondary hypertension. Suzuki et al found an increase in LV end-diastolic diameter, but no difference in wall thickness or LV mass in 19 PA patients compared with 19 renovascular hypertensive patients. More recently, Rossi et al reported on 34 PA patients compared with 34 EH controls, and showed increased posterior wall and interventricular septal thickness, as well as increased LV mass in the PA group; however, LV mass was not indexed by height in that report. Moreover, none of these studies addressed LV contractile function using the midwall fractional shortening circumferential end-systolic stress relation.

Weber et al, based on studies in the rat in which aldosterone secretion was elevated secondary to renal artery stenosis and in which deleterious effects of aldosterone were interrupted by spironolactone, have proposed that aldosterone can induce extracellular matrix and collagen deposition in the myocardium. This raised the possibility that aldosterone excess in PA could result in fibrosis, an increase in LV mass, and potentially in alterations in LV contractility or diastolic function. In this study, we have found no evidence in human patients to support the association between increased aldosterone and either LV hypertrophy or systolic dysfunction suggested by this hypothesis. Because the groups were well matched for BP and other relevant variables, any differences in LV geometry or contractility should reflect the unique effects of aldosterone on LV structure and function. However, no such differences were observed.

One limitation of this study is that it did not assess measures of LV diastolic filling or stiffness. At present, it remains possible that unique differences in PA patients may only be observed in diastolic function, perhaps reflecting an increase of the extracellular fibrotic component of the myocardium due to exposure to increased aldosterone levels. Further research to examine the associations between aldosterone and LV diastolic filling and stiffness will be needed to resolve this question.

Acknowledgment
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