Arterial Pressure, Left Ventricular Mass, and Aldosterone in Essential Hypertension

Areeg H. El-Gharbawy, Vishwanatha S. Nadig, Jane Morley Kotchen, Clarence E. Grim, Kiran B. Sagar, Mary Kaldunski, Pavel Hamet, Zdenka Pausova, Daniel Gaudet, Francis Gossard, Theodore A. Kotchen

Abstract—The purpose of the present study was to evaluate the relationship of aldosterone to blood pressure and left ventricular size in black American (n=109) and white French Canadian (n=73) patients with essential hypertension. Measurements were obtained with patients off antihypertensive medications and included 24-hour blood pressure monitoring, plasma renin activity and aldosterone, and an echocardiogram. Compared with the French Canadians, the black Americans had higher body mass indexes, higher systolic blood pressures, attenuated nighttime reduction of blood pressure, and lower serum potassium concentrations (P<0.01 for each). Left ventricular mass index, posterior wall thickness, interventricular septal thickness, and relative wall thickness were also greater (P<0.01 for each) in the black American patients. Supine and standing plasma renin activity was lower (P<0.01 and P<0.05, respectively) in the black Americans, whereas supine plasma aldosterone concentrations did not differ, and standing plasma aldosterone was greater (P<0.05) in the black Americans (9.2±0.7 ng/dL) than in the French Canadians (7.3±0.6 ng/dL). In the black Americans, supine plasma aldosterone was positively correlated with nighttime systolic (r=0.30; P<0.01) and diastolic (r=0.39; P<0.001) blood pressures and inversely correlated with the nocturnal decline of systolic (r=-0.29; P<0.01) and diastolic (r=-0.37; P<0.001) blood pressures. In the black Americans, standing plasma aldosterone was positively correlated with left ventricular mass index (r=0.36; P<0.001), posterior wall thickness (r=0.33; P<0.01), and interventricular septal thickness (r=0.26; P<0.05). When the black American patients were divided into obese and nonobese groups, significant correlations between plasma aldosterone and both blood pressure and cardiac mass were observed only in the obese. In the French Canadians, overall, plasma aldosterone did not correlate with either blood pressure or any measures of heart size. However, among obese French Canadians, supine plasma aldosterone correlated with nighttime diastolic (r=0.53, P<0.02) and systolic (r=0.44, P<0.01) blood pressures but not with cardiac mass. These results are consistent with the hypothesis that aldosterone contributes to elevated arterial pressure in obese black American and obese white French Canadian patients with essential hypertension and to the attenuated nocturnal decline of blood pressure and left ventricular hypertrophy in obese, hypertensive black Americans. (Hypertension. 2001;37:845-850.)

Key Words: race ■ aldosterone ■ echocardiography ■ left ventricle ■ obesity ■ plasma renin activity

Aldosterone is a potent mineralocorticoid that promotes sodium retention and elevation of arterial pressure. Independent of its effect on blood pressure, aldosterone may also play a role in cardiac hypertrophy. Within the myocardium, aldosterone acts via mineralocorticoid receptors to enhance extracellular matrix and collagen deposition.1 In animal models, both cardiac load and high circulating aldosterone levels stimulate fibrosis within the myocardium, leading to left ventricular hypertrophy (LVH).2 Pathological patterns of LV geometry have also been associated with elevations of plasma aldosterone concentrations in patients with essential hypertension,3,4 and the early onset of LVH has been described in patients with primary aldosteronism.5

The prevalence of hypertension in US blacks is 50% greater than that in whites in either the United States or Canada.6,7 Plasma renin activity (PRA) tends to be suppressed in hypertensive blacks,3 and blacks have a high prevalence of salt-sensitive hypertension.9 In addition, among hypertensives, blacks have a higher prevalence of LVH and a 6-fold higher prevalence of concentric LV remodeling than do whites.10–14 The purpose of the present study was to evaluate the relationship of aldosterone to both blood pressure and LV geometry in both black and white patients with essential hypertension.

Methods

In conjunction with ongoing collaborative studies of the genetic determinants of hypertension, black American patients were studied...
at the Medical College of Wisconsin in Milwaukee and white French Canadian patients were studied in Chicoutimi Hospital, located in the Saguenay-Lac St Jean region of Canada. Identical protocols were carried out at inpatient clinical research centers at both sites. Standardization was ensured by periodic visits and teleconferences between investigators at both sites. The protocols were approved by the appropriate human investigation committees at both participating institutions.

Consenting patients aged 18 to 55 years with essential hypertension were potential candidates for the study. Black American subjects were recruited from the medical clinics associated with the Medical College of Wisconsin and from a variety of community-based screenings. White French Canadian patients were recruited from clinics associated with Chicoutimi Hospital. Subjects were considered to have hypertension if standardized outpatient measurements of blood pressure were >140/90 mm Hg on 2 occasions or if they were taking antihypertensive medications. Exclusion criteria included secondary hypertension, serum creatinine >2.2 mg/dL, diastolic blood pressure >110 mm Hg on drug therapy, diabetes mellitus, body mass index (BMI) >34 kg/m², pregnancy, malignancy, substance abuse (including alcohol), and myocardial infarction or stroke within 6 months. Before the study, antihypertensive drugs were withdrawn for ≥1 week.

At both sites, patients were admitted to an inpatient clinical research center and were placed on a weight-maintenance diet that included 150 mEq Na+/d and 80 mEq K+/d. Anthropomorphic measurements included height, weight, waist and hip circumferences, and skinfold thickness at multiple sites. After overnight recumbency, baseline measurements included basic chemistry and measurements of PRA and plasma aldosterone concentration after 60 minutes in the supine position and again after standing for 10 minutes. Blood pressure was measured over a 24-hour period with an Accutracker every 20 minutes during the daytime (5 AM to 11 PM) and every 45 minutes during the nighttime (11 PM to 5 AM). In addition, a 2-dimensional echocardiogram was obtained.

All measurements of PRA and plasma aldosterone were carried out in the same core laboratory. PRA was determined according to a modification of the method of Sealey and Laragh, with angiotensin I antiserum kindly provided by Dr Jean Sealey.15 Aldosterone was measured by radioimmunoassay with a commercially available assay kit (Coat-a-Count Aldosterone; Diagnostic Products Corp). In our laboratory, the interassay coefficients of variation for the commercially available low and high aldosterone pools are 10.2% and 9.2%, respectively. The respective intra-assay coefficients of variation are 5.1% and 4.4%.

Two-dimensional echo-guided M-mode tracings (Sonos 2500; Hewlett Packard) were obtained during diastole at or just below the tips of the mitral valve leaflets. Measurements of LV internal diameter (LVId), intraventricular septal thickness (IST), and posterior wall thickness (PWT) were obtained according to the guidelines of the American Society of Echocardiography.16,17 LV mass (LVM) was calculated from averaged measurements with the formula:

\[ \text{LVM} = 1.04[(\text{IST} + \text{PWT} + \text{LVId})^3 - (\text{LVId})^3] - 14 \text{ g} \]

LVM was normalized to body surface area for determination of LVM index (LVMI). Relative wall thickness (RWT) was measured at end diastole as the ratio 2 PWT/LVId.19

Two-way ANOVA was used to evaluate the statistical significance of differences between subject populations (black American and white French Canadian). The significance of 2 group comparisons was determined with a 2-tailed, unpaired \( t \) test for normally distributed variables and with the Mann-Whitney rank test for variables that were not normally distributed. A paired \( t \) test was used to evaluate the significance of the effect of a maneuver (eg, posture) or time of day on a variable. Pearson’s correlation analyses were used to evaluate the relationships between plasma aldosterone, LV size, and blood pressure. The Spearman rank correlation was used when variables were not normally distributed. Multivariate analysis was used for adjustment of potentially confounding variables. The significance of percent differences in the 2 subject populations was determined with a \( \chi^2 \) test. \( P<0.05 \) was considered to be statistically significant. Results are presented as mean±SEM.

### TABLE 1. Comparison of Clinical Characteristics in the 2 Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Black Americans</th>
<th>French Canadians</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=109; 70F, 39M)</td>
<td>(n=73; 30F, 43M)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td>44.5±0.6</td>
<td>49.2±0.6**</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>30.6±0.5</td>
<td>27.0±0.8**</td>
</tr>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>140±1</td>
<td>142±1</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>3.8±0.1</td>
<td>4.6±0.5**</td>
</tr>
<tr>
<td><strong>Daytime BP, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>143±2</td>
<td>134±3**</td>
</tr>
<tr>
<td>DBP</td>
<td>86±1</td>
<td>84±2</td>
</tr>
<tr>
<td><strong>Nighttime BP, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>136±2</td>
<td>122±3**</td>
</tr>
<tr>
<td>DBP</td>
<td>80±1</td>
<td>76±2</td>
</tr>
<tr>
<td><strong>Day minus night BP, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>8±1</td>
<td>13±2**</td>
</tr>
<tr>
<td>DBP</td>
<td>6±1</td>
<td>8±1*</td>
</tr>
<tr>
<td><strong>Cardiac dimensions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM, gm/m²</td>
<td>123±5</td>
<td>86±2**</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>11.7±0.2</td>
<td>8.8±0.1**</td>
</tr>
<tr>
<td>IST, mm</td>
<td>12.1±0.3</td>
<td>9.6±0.2**</td>
</tr>
<tr>
<td>RWT</td>
<td>0.52±0.01</td>
<td>0.37±0.01**</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. *\( P<0.05 \); **\( P<0.01 \).

### Results

A total of 109 black Americans (39 men and 70 women) and 73 white French Canadians (43 men and 30 women) participated in the study (Table 1). There was some variation in the number of subjects for the different measurements because not all measurements were obtained in all subjects. The black American patients were younger and had a higher BMI than the French Canadians (\( P<0.01 \) for both). Serum sodium and creatinine concentrations did not differ in the 2 groups, and serum potassium concentration was lower (\( P<0.01 \)) in the black Americans. Among the black Americans, serum potassium concentrations did not differ between those who had previously been taking diuretics and those who had not. Based on 24-hour blood pressure monitoring, average daytime systolic blood pressure was higher (\( P<0.01 \)) in the black Americans, although average daytime diastolic blood pressures did not differ in the 2 patient groups. Within each group, average nighttime blood pressures were lower (\( P<0.001 \)) than daytime blood pressures, but the nighttime reduction in blood pressure was less (\( P<0.05 \)) in the black Americans than in the French Canadians. Nighttime systolic and diastolic blood pressures of the black Americans were higher (\( P<0.01 \) and \( P<0.05 \), respectively) than those of the French Canadians.

In both groups, PRA and plasma aldosterone increased (\( P<0.001 \) for both) in response to upright posture. PRA was lower in the black Americans than in the French Canadians in the supine (\( P<0.01 \)) and standing (\( P<0.05 \)) positions (Figure 1). Supine plasma aldosterone concentrations did not differ...
between the 2 groups, although standing plasma aldosterone was higher \( (P<0.05) \) in the black Americans. In both the supine and standing positions, the plasma aldosterone/PRA ratio was higher \( (P<0.01) \) in the black Americans. In addition, in response to upright posture, the increase of aldosterone was greater \( (P<0.001) \) in the black Americans than in the French Canadians, and the ratio of the increment of aldosterone to the increment of PRA was also greater \( (P<0.05) \) in the black Americans. Among black American women, supine plasma aldosterone was significantly correlated with BMI \( (r=0.26, P<0.05), \) body surface area \( (r=0.27, P<0.05), \) waist circumference \( (r=0.23, P<0.02), \) and hip circumference \( (r=0.23, P<0.02) \) but not with waist-to-hip ratio or with percent body fat (determined from measurements of skinfold thickness). There were no significant correlations of plasma aldosterone with any of the these anthropomorphic measurements in black American men or in the French Canadian women or men.

Among the black Americans, there were several significant positive correlations between plasma aldosterone and blood pressure (Table 2). Supine plasma aldosterone was significantly correlated with nighttime systolic \( (P<0.01) \) and diastolic \( (P<0.001) \) blood pressures. Figure 2A depicts the regression of supine plasma aldosterone with sleeping diastolic blood pressure. Supine plasma aldosterone was also inversely correlated with the daytime-minus-nighttime differences of systolic \( (P<0.01) \) and diastolic \( (P<0.001) \) blood pressures (ie, the higher the plasma aldosterone, the less the nighttime reduction in blood pressure). Also in the black Americans, standing plasma aldosterone was positively correlated with nighttime diastolic blood pressure \( (P<0.05) \). In contrast, among the French Canadians, there were no significant correlations between plasma aldosterone and blood pressure. PRA did not correlate with blood pressures in either patient group.

The following cardiac dimensions were greater \( (P<0.001) \) in the black Americans than in the white French Canadians: LVMI, IST, PWT, and RWT (Table 1). Overall, LVH was observed in 88% of the black American patients and in 23% of the white French Canadian patients \( (P<0.001) \). Based on a partition value of 0.45, the mean RWT of 0.52±0.01 in black Americans is consistent with LV concentric remodeling. \(^{18}\) Among the patients with LVH, the prevalence of concentric hypertrophy in the black American and white French Canadian patients was 50% and 9%, respectively \( (P<0.001) \). In both the black Americans and the white French Canadians, LVMI, PWT, and IST were significantly correlated with 24-hour systolic blood pressures \( (all P<0.05) \). In the French Canadians, there also was a significant correlation between systolic blood pressure and RWT \( (r=0.52, P<0.01) \). In contrast, in the black Americans, RWT was not correlated with blood pressure. However, in a multivariate analysis, the differences in cardiac dimensions in the 2 patient groups remained significant after adjustment for the differences in blood pressure and BMI.

Among the black Americans, there were several significant correlations between plasma aldosterone and cardiac dimensions (Table 2). Supine plasma aldosterone was correlated with PWT \( (P<0.05) \) and RWT \( (P<0.02) \). Standing plasma aldosterone was correlated with LVMI \( (P<0.001) \), PWT \( (P<0.01) \), and IST \( (P<0.05) \). Figure 2B depicts the regression of standing plasma aldosterone with LVMI. In contrast,
there was an inverse correlation between supine PRA and LVMI in the black Americans ($r=-0.24; P<0.05$). In multiple linear regression analyses, the relationships of both plasma aldosterone and PRA with cardiac dimensions were not accounted for by either blood pressure or gender. None of the measured cardiac dimensions correlated with either PRA or plasma aldosterone in the French Canadian patients.

Because the mean BMI of the black Americans was greater than that of the white French Canadians, to evaluate the effect of obesity on the relationships of aldosterone to both blood pressure and cardiac mass, patients were divided into obese ($\text{BMI} \geq 27 \text{ kg/m}^2$) and nonobese ($\text{BMI} < 27 \text{ kg/m}^2$) groups. Based on this criterion, 74% of the black American patients and 50% of the French Canadian patients were obese. Within each population, blood pressures and cardiac dimensions did not differ between obese and nonobese patients. PRA, plasma aldosterone, and the plasma aldosterone/PRA ratio also did not differ between obese and nonobese subjects.

In the obese black Americans, supine plasma aldosterone was significantly correlated with nighttime diastolic ($r=0.46, P<0.0003$) and systolic ($r=0.33, P<0.01$) blood pressures, daytime diastolic blood pressure ($r=0.22, P<0.07$), and daytime-minus-nighttime diastolic ($r=-0.41, P<0.01$) and systolic ($r=-0.31, P<0.02$) blood pressures. There were no significant correlations between plasma aldosterone and blood pressure in the nonobese black Americans. Similarly, among the obese French Canadians, supine plasma aldosterone was significantly correlated with nighttime diastolic ($r=0.53, P<0.02$) and systolic ($r=0.44, P<0.01$) blood pressures, whereas there were no significant correlations between plasma aldosterone and blood pressure in the nonobese French Canadians. In addition, in obese black Americans, standing plasma aldosterone was significantly correlated with LVM ($r=0.39, P<0.003$) and PWT ($r=0.38, P<0.005$), and standing plasma aldosterone was correlated with PWT ($r=0.31, P<0.03$) and RWT ($r=0.35, P<0.01$). There were no significant correlations between plasma aldosterone and any of these cardiac dimensions in nonobese black Americans (Figure 3) or in either obese or nonobese French Canadians.

**Discussion**

In conjunction with our ongoing studies of the genetic determinants of hypertension, we developed standardized protocols to evaluate patients with essential hypertension in 2 distinct populations: black Americans and a genetically and geographically isolated white French Canadian population in the Saguenay-Lac St Jean region of Canada. This allowed us to identify phenotypic similarities and differences in these 2 patient populations. In the present report, we confirm that black hypertensives have relatively high plasma aldosterone concentrations in relation to low PRA, compared with white hypertensives. Supine plasma aldosterone was significantly correlated with nighttime blood pressures in obese patients of each population. In addition, plasma aldosterone was inversely related to the difference between daytime and nighttime blood pressures and positively related to cardiac dimensions in the obese black Americans but not in the obese French Canadians. These observations suggest that adiposity and race modify the relationship of aldosterone with both blood pressure and LVM.

In normotensive children and adults, PRA, plasma aldosterone, and urine aldosterone excretion are lower in blacks than in whites. Among hypertensives, however, most reports indicate that despite the suppression of PRA in blacks, plasma aldosterone and/or urine aldosterone excretion do not differ between blacks and whites. Similarly, in the present study, although PRA was lower among hypertensive black Americans than among hypertensive white French Canadians, supine plasma aldosterone did not differ in the 2 groups and standing plasma aldosterone was higher in the black Americans. In addition, among black American women, supine plasma aldosterone was correlated with BMI. Other investigators have also reported an association between aldosterone and obesity, particularly visceral obesity. This relationship has been observed more consistently in women than in men, and Goodfriend et al speculated that visceral fat may in some way stimulate adrenal steroidogenesis.
The increased plasma aldosterone/PRA ratios and the greater increment of plasma aldosterone per increment of PRA in response to upright posture suggest that these hypertensive black Americans have an increased adrenal sensitivity to endogenous angiotensin II. Other investigators have reported that patients with low-renin essential hypertension who consume a normal or “liberal” NaCl intake have augmented aldosterone responses to either endogenous renin-angiotensin or the infusion of angiotensin II. However, on a low NaCl intake (10 mEq/d), Fisher et al. reported that hypertensive blacks (both normal-renin and low-renin patients) and low-renin hypertensives (both blacks and whites) have blunted aldosterone responses to both upright posture and the infusion of angiotensin II, possibly due to an abnormality of angiotensin receptor number or affinity. The augmented aldosterone response to angiotensin II on a liberal NaCl diet may be more relevant to the regulation of aldosterone secretion under usual, free-living conditions.

Patients with idiopathic primary hyperaldosteronism also have enhanced aldosterone responsiveness to angiotensin II. It has been proposed that idiopathic hyperaldosteronism and low-renin “essential” hypertension are not distinct clinical entities but rather are pathogenetically related and differ only in the level of aldosterone production. Consistent with this hypothesis, similar polymorphisms of the aldosterone synthase gene have been observed in patients with idiopathic primary aldosteronism and patients with low-renin essential hypertension.

Previous reports indicate either no correlation or weakly positive correlations between plasma aldosterone and blood pressure in white patients with essential hypertension. We observed that plasma aldosterone was positively correlated with nighttime blood pressures in obese black American and obese French Canadian hypertensives but not in nonobese patients of either population. Consistent with previous reports, the nighttime reduction in blood pressure was attenuated in the hypertensive black Americans compared with the white French Canadian hypertensive patients. Further, there was an inverse association between plasma aldosterone and the nighttime reduction in blood pressure in the obese black Americans but not in the French Canadians. Taken together, these observations are consistent with the hypothesis that aldosterone contributes to elevated nighttime arterial pressure in obese black American and obese white French Canadian patients with essential hypertension and to the attenuated nocturnal decline of blood pressure in obese, hypertensive black Americans.

LVM is a powerful predictor of cardiovascular morbidity and mortality, independent of blood pressure and other known risk factors. Several studies report greater LVM and a higher prevalence of LVH among hypertensive blacks than among whites. Black hypertensives also have an increased prevalence of concentric remodeling and concentric hypertrophy of the LV. Consistent with these previous reports, we observed that LVM, RWT, PWT, and IST, as well as the prevalence of concentric hypertrophy and remodeling, were greater in the black American than the French Canadian hypertensives. These alterations of LVM and geometry were associated with plasma aldosterone concentra-

ions in the obese, but not the nonobese, black Americans. In contrast, in the French Canadian patients, there was a low prevalence of LVH, and LVM was not associated with plasma aldosterone in either obese or nonobese subjects. Similar to these results in the French Canadians, Schlaich et al. recently reported that there was no association of plasma or urine aldosterone with LVM in young white men with mild essential hypertension. However, they did observe an association between LVM and incomplete aldosterone suppression after a 1-week period of oral salt loading.

Experimental and clinical observations with spironolactone, a mineralocorticoid antagonist, highlight the potentially adverse effects of aldosterone on cardiac structure and function. In the rat, spironolactone prevents aldosterone-induced myocardial fibrosis. In a multicenter trial of 1663 patients with symptomatic congestive heart failure, the overall risks of death, death due to progressive heart failure, and sudden death from cardiac causes were reduced by 30% among spironolactone-treated patients.

In conclusion, the hypertensive black American patients in this study had “inappropriate” elevations of plasma aldosterone in relation to low PRA compared with the white patients with essential hypertension. Serum potassium concentrations were also lower in the black American patients. Nighttime blood pressures were correlated with plasma aldosterone in the obese black American and obese French Canadians. In addition, LV size and geometry were correlated with plasma aldosterone in the obese black Americans but not in the obese white French Canadians. These observations are consistent with the hypothesis that aldosterone contributes to elevated arterial pressure in obese black American and obese white patients with essential hypertension and to LVH in obese, black American hypertensives.

Acknowledgments
This study was supported by US Public Health Service grants P50 HL-54998 and 5-M01-RR-00058 (General Clinical Research Center).

References


Arterial Pressure, Left Ventricular Mass, and Aldosterone in Essential Hypertension
Areeg H. El-Gharbawy, Vishwanatha S. Nadig, Jane Morley Kotchen, Clarence E. Grim, Kiran B. Sagar, Mary Kaldunski, Pavel Hamet, Zdenka Pausova, Daniel Gaudet, Francis Gossard and Theodore A. Kotchen

Hypertension. 2001;37:845-850
doi: 10.1161/01.HYP.37.3.845

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/37/3/845

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/