Regulation of Aldosterone Secretion in Hypertensive Blacks

Naomi D.L. Fisher, Ray E. Gleason, Thomas J. Moore, Gordon H. Williams, Norman K. Hollenberg

Abstract  Hypertension in blacks is common, often severe, and largely unexplained. Recent studies have suggested that aldosterone secretion in blacks may be reduced, whereas older data demonstrate no racial differences in aldosterone excretion. We performed this study to examine adrenal responsiveness in black hypertensive patients under controlled metabolic conditions. Thirty-one black hypertensive patients and 7 black normotensive subjects were studied on intakes of 10 mmol/d sodium and 100 mmol/d potassium, with the renin-angiotensin-aldosterone system further stimulated by upright posture or infusion of angiotensin II (Ang II). Forty-six hypertensive and 14 normotensive whites underwent the same protocol as a comparison group. Hypertensive blacks and whites had similar mean basal plasma aldosterone levels on a low salt diet, lower in both groups than in normotensive subjects. In the black patients, however, plasma aldosterone responses were significantly lower than responses in white hypertensive patients when further stimulated by either posture (1451±216 versus 2571±225 pmol/L [52.3±7.8 versus 92.7±8.1 ng/dL], P<.002) or Ang II infusion (843±122 versus 1617±189 pmol/L [30.4±4.4 versus 58.3±6.8 ng/dL], P<.001). Renin status did not account for the difference. Basal and stimulated plasma aldosterone concentrations, on the other hand, were similar in normotensive white and black subjects. Blunted adrenal responses to upright posture and Ang II infusion are common among black hypertensive patients. These abnormalities may be part of a larger constellation of abnormalities in blacks, reflecting perhaps a greater, more frequent underlying disturbance in salt handling than in whites. (Hypertension. 1994;23:179-184.)

Key Words  • angiotensin II • renin • posture • sodium • potassium • aldosterone • blacks

Hypertension in blacks is common and often severe yet remains poorly understood.1,4 In response to suggestions of an increased incidence of primary aldosteronism in blacks,2 a comparative study found no difference in aldosterone excretion between black and white normotensive subjects or hypertensive patients.6 Recently, a reduction in aldosterone secretion was documented in black children, with strong familial influences on the aldosterone excretion rate.7,8 The following description results from a systematic assessment of adrenal responsiveness in blacks, using three stimuli known to increase aldosterone secretion: restriction of sodium intake, upright posture, and angiotensin II (Ang II) infusion.

Methods

We studied 31 black patients (14 men, 17 women) with hypertension and 7 black normotensive men. Race was determined by self-identification and supported by physical appearance. The term “black” is used instead of “African American” because not all of the patients were American.

Forty-six white hypertensive patients, matched with the black patients for age, gender, and body mass index, served as the comparison group. Although this group consisted of proportionately fewer women (Table 1), the difference was not statistically significant (χ2=1.26). Fourteen white normotensive men were also matched for comparative study.

Hypertension was defined as a systolic blood pressure greater than 140 mm Hg and a diastolic blood pressure greater than 90 mm Hg on at least three outpatient visits. Antihypertensive medications if previously used were discontinued at least 2 weeks before study.

On admission to the metabolic ward, each subject was placed on a constant isocaloric diet of 10 mmol NaCl and 100 mmol potassium, with 2000 mL of water per day. Daily 24-hour urine collections were obtained for measurement of sodium, potassium, and creatinine. After 4 to 6 days, when external sodium balance had been achieved, upright posture studies and Ang II infusions were performed on separate days. Each study began at 8 AM after the subjects had been fasting and recumbent for at least 8 hours.

Protocols

Each patient’s renin status was determined on the basis of plasma renin activity (PRA) after 2 hours in the upright position. Low-renin hypertension was defined by a PRA of less than 0.69 ng/L per second (2.5 ng Ang I/mL per hour) at the end of the posture study.

While remaining in low-salt balance, each patient received an infusion of Ang II amide (CIBA-GEIGY, Summit, NJ) at 3 ng/kg minute for 40 to 45 minutes delivered by an infusion pump (Harvard Apparatus, Millis, Mass). The dose of 3 ng/kg per minute was used because it has been found to stimulate aldosterone release with minimal pressor effects. Blood was drawn for measurement of PRA and plasma aldosterone, cortisol, and Ang II concentrations before and at the end of the Ang II infusion. During the infusion, blood pressure was monitored every 2 minutes with an indirect recording sphygmomanometer. In one patient the Ang II infusion was discontinued because of an exaggerated pressor response; in all other subjects the changes in blood pressure during the infusion were minor.

Laboratory and Statistical Procedures

All blood samples were collected on ice and centrifuged immediately; the plasma was then separated and frozen until
the time of assay. Serum and urinary sodium and potassium levels were measured by flame photometry using lithium as an internal standard. Serum and urine creatinine concentrations were measured by an autoanalyzer technique. PRA, plasma Ang II, aldosterone, and plasma cortisol were measured by radioimmunoassay techniques previously described.9,10

Any patient who demonstrated a rise in plasma cortisol of 221 nmol/L (8 μg/dL) or greater during either the posture study or Ang II infusion was excluded from analysis by Chauvenet's criterion to avoid the possible confounding factor of adrenocorticotropin (ACTH) as a separate stimulus for aldosterone release in these subjects. Data from five black and nine white patients were excluded from initial analysis for this reason, but a comprehensive analysis including all of these points was also performed and is reported below.

The study protocols were approved by the Human Subjects Committee of the Brigham and Women's Hospital, and informed, written consent was obtained from each subject.

Group means have been presented with the standard error of the mean as the index of dispersion. Alpha levels less than or equal to .05 were considered statistically significant. Differences between means of variables measured in blacks and whites were tested for significance using unpaired t tests when data were normally distributed, and differences between medians via the Wilcoxon rank sum test when they were not. The unpaired t tests were also adjusted for unequal variances when appropriate. Data from hypertensive and normotensive subjects were analyzed separately. Data entry and analyses were performed using the CLINFO and SAS software packages, respectively.

Results

The black and white hypertensive patients were well matched for mean age, weight, body mass index, renal function, and serum electrolytes (Table 1). Admission blood pressure tended to be somewhat higher in blacks than whites, but the difference did not achieve statistical significance. Five of the blacks and four of the whites had a diastolic blood pressure exceeding 110 mm Hg. To ascertain whether a higher blood pressure could have contributed to blunting of the aldosterone response, we assessed symmetry about the median response in blacks and could identify no difference in the frequency of blunted responses in those with the highest and those with the lowest blood pressure. Mean 24-hour urinary sodium levels on the day before study were also not statistically different between the blacks and whites. Potassium excretion tended to be lower in blacks than whites (69.6±5.3 versus 80.1±3.1 mmol/24 h) despite identical intake, although the difference did not reach statistical significance. Mean basal plasma cortisol concentrations were somewhat variable and did not differ between the races (Tables 1 through 3).

Black and white normotensive subjects had similar mean age, weight, and body mass index, although they were younger than the hypertensive patients (average age, 30.3 years for the blacks and 31.4 for the whites) and leaner (body mass index, 22.8 and 23.5 kg/m², respectively). Blood pressure in low-salt balance, renal function, and serum and urinary electrolytes did not differ between the two groups of normotensive subjects.

Hypertensive patients had lower recumbent aldosterone levels on a low salt diet than did normotensive subjects, regardless of race. Mean baseline aldosterone values among hypertensive patients were significantly lower before Ang II infusion (596±58 versus 1032±111 pmol/L [21.5±2.1 versus 37.2±4.0 ng/dL], P<.0005) and also before posture study (602±44 versus 877±169 pmol/L [21.7±1.6 versus 31.6±6.1 ng/dL], P<.04 (Figs 1 and 2). Despite an identical rise in PRA in black and white hypertensive patients in response to upright posture (Table 2), the mean increment in plasma aldosterone concentration in the blacks was significantly less than in the whites (849±169 versus 1967±205 pmol/L [30.6±6.1 versus 70.9±7.4 ng/dL], P<.0001, Fig 1). An essentially identical difference was found when all patients with a rise in cortisol were included (aldosterone increment in whites, 863±147 pmol/L versus 1922±189 in blacks [31.1±5.3 versus 69.3±6.8 ng/dL], P<.0001). Low-renin hypertension was identified in 8 of the 31 black patients (29%) and

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Information</th>
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<table>
<thead>
<tr>
<th></th>
<th>Normotensive Subjects</th>
<th>Hypertensive Patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Males</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Age, y</td>
<td>30.3±3.6</td>
<td>31.4±2.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.5±2.8</td>
<td>76.7±2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.8±1.1</td>
<td>23.5±0.6</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>110±4</td>
<td>104±3</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70±3</td>
<td>67±2</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>97±3</td>
<td>97±2</td>
</tr>
<tr>
<td>Serum sodium, mmol/L*</td>
<td>137±1</td>
<td>140±2</td>
</tr>
<tr>
<td>Serum potassium, mmol/L*</td>
<td>4.1±0.2</td>
<td>4.2±0.06</td>
</tr>
<tr>
<td>Serum cortisol, nmol/L*</td>
<td>382±41</td>
<td>441±55</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 hours*</td>
<td>9.9±1.8</td>
<td>8.2±1.8</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 hours*</td>
<td>9.6±6.2</td>
<td>9.4±19.5</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.
*When balance achieved on a 10 mEq sodium intake.
†P<.03.
TABLE 2. Response to Postural Stimulus In Hypertensive Patients

<table>
<thead>
<tr>
<th>Renin Status</th>
<th>Blacks</th>
<th></th>
<th></th>
<th>Whites</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=21)</td>
<td>Low (n=5)</td>
<td></td>
<td>Normal (n=33)</td>
<td>Low (n=4)</td>
<td></td>
</tr>
<tr>
<td>PRA, (ng/L)/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Recumbent</td>
<td>4.0±0.6</td>
<td>1.0±0.3</td>
<td></td>
<td>3.1±0.3</td>
<td>0.8±0.3</td>
<td></td>
</tr>
<tr>
<td>Standing (2 hours)</td>
<td>9.2±1.3</td>
<td>1.4±0.4</td>
<td></td>
<td>8.6±0.8</td>
<td>1.4±0.4</td>
<td></td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recumbent</td>
<td>599±89</td>
<td>358±83</td>
<td></td>
<td>605±50</td>
<td>655±422</td>
<td></td>
</tr>
<tr>
<td>Standing (2 hours)</td>
<td>1451±216</td>
<td>976±275</td>
<td></td>
<td>2571±225</td>
<td>1714±591</td>
<td></td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recumbent</td>
<td>480±55</td>
<td>502±91</td>
<td></td>
<td>386±22</td>
<td>359±132</td>
<td></td>
</tr>
<tr>
<td>Standing (2 hours)</td>
<td>417±52</td>
<td>450±66</td>
<td></td>
<td>381±19</td>
<td>579±298</td>
<td></td>
</tr>
</tbody>
</table>

PRA indicates plasma renin activity.

in 5 of the 46 white patients (11%). When subjects in only the low-renin category were considered, blacks again displayed a blunted response compared with whites (619±230 versus 1215±158 pmol/L [22.3±8.3 versus 43.8±5.7 ng/dL]), but the differences were not significant because of small sample size and variability (Table 2). In the normotensive subjects tested with upright posture, blacks and whites demonstrated similar baseline and stimulated aldosterone values (Fig 1).

After Ang II infusion, which yielded similar plasma Ang II levels in both races (Table 3), the rise in plasma aldosterone in the black hypertensive patients was significantly less than in the whites (283±75 versus 1004±161 pmol/L [10.2±2.7 versus 36.2±5.8 ng/dL], P<.0002, Fig 2). Again, essentially identical results were obtained when all patients with a rise in cortisol were included (P<.0001). The patterns of response in the low-renin patients were similar, but as with the posture stimulus these trends did not reach statistical significance. Ang II infusion at 3 ng/kg per minute in black and white normotensive subjects resulted in similar rises in plasma Ang II levels and concordant increases in plasma aldosterone (485±222 versus 502±105 pmol/L [17.5±8.0 versus 18.1±3.8 ng/dL], Fig 2).

Individual aldosterone responses to infused Ang II in the hypertensive patients varied over a wide range (Fig 3). In the 18 blacks with a normal renin status, 13 (72%) had a rise that was less than 20 ng/dL, compared with 14 of 37 whites (38%, P<.025).11

Discussion

Our study documented two abnormalities in aldosterone secretion. First, hypertensive patients of both races had lower plasma aldosterone levels than did normotensive subjects when recumbent and on a sodium-restricted diet. Second, when aldosterone secretion was

TABLE 3. Response to Angiotensin II Infusion In Hypertensive Patients

<table>
<thead>
<tr>
<th>Renin Status</th>
<th>Blacks</th>
<th></th>
<th></th>
<th>Whites</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=18)</td>
<td>Low (n=8)</td>
<td></td>
<td>Normal (n=37)</td>
<td>Low (n=5)</td>
<td></td>
</tr>
<tr>
<td>PRA, (ng/L)/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>5.0±0.8</td>
<td>1.9±0.7</td>
<td></td>
<td>3.9±0.5</td>
<td>0.9±0.2</td>
<td></td>
</tr>
<tr>
<td>Ang II infusion</td>
<td>4.5±0.9</td>
<td>1.9±0.8</td>
<td></td>
<td>3.0±0.4</td>
<td>0.7±0.2</td>
<td></td>
</tr>
<tr>
<td>Ang II, fmol/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Basal</td>
<td>32±4</td>
<td>23±1</td>
<td></td>
<td>30±2</td>
<td>33±7</td>
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<tr>
<td>Ang II infusion</td>
<td>73±9</td>
<td>58±13</td>
<td></td>
<td>60±5</td>
<td>71±7</td>
<td></td>
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<tr>
<td>Aldosterone, pmol/L</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Basal</td>
<td>560±89</td>
<td>402±97</td>
<td></td>
<td>613±78</td>
<td>788±283</td>
<td></td>
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<tr>
<td>Ang II infusion</td>
<td>843±122</td>
<td>741±136</td>
<td></td>
<td>1617±189</td>
<td>1315±366</td>
<td></td>
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<tr>
<td>Cortisol, nmol/L</td>
<td></td>
<td></td>
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<tr>
<td>Basal</td>
<td>326±33</td>
<td>276±41</td>
<td></td>
<td>400±25</td>
<td>361±77</td>
<td></td>
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<tr>
<td>Ang II infusion</td>
<td>295±25</td>
<td>279±63</td>
<td></td>
<td>315±19</td>
<td>317±66</td>
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PRA indicates plasma renin activity; Ang II, angiotensin II.
further stimulated with either upright posture or Ang II infusion, black hypertensive patients exhibited signifi-
cantly smaller aldosterone responses than whites. Among normotensive subjects, stimulated plasma al-
dosterone levels were similar in blacks and whites; this responsiveness was consistent with previously published
normotensive data from our group. Thus, the abnormal 
adrenal responsiveness did not reflect race alone but rather the entity of hypertension in blacks. The renin-
angiotensin-aldosterone system is least stimulated when extracellular fluid volume is replete; we did not examine
this state. Pratt et al., however, found lower urinary and plasma aldosterone concentrations among black chil-
dren who were consuming their usual diets (mean urinary sodium excretion, 0.66 mmol per micromole 
creatinine per kilogram). Salt restriction provided us
with the first indication of abnormal adrenal responsive-
ness: the adrenal response to a low salt diet was less in hypertensive patients than in normotensive subjects but
did not differ in blacks and whites. Dustan and cowork-
ers measured aldosterone excretion rate in hyperten-
sive patients on a diet of 10 mmol sodium and also
found no significant difference between blacks and whites. Sowers et al. found similar levels of plasma 
aldosterone among normotensive and hypertensive
black men on a diet of 40 mmol sodium per day and
concluded that salt-sensitive hypertension in blacks is
commonly attributed to lower potassium intake. Blacks
and whites. Previous studies have demonstrated lower 
rates of renal potassium excretion among blacks,
commonly attributed to lower potassium intake. Blacks

Aldosterone response to an upright posture

Aldosterone response to an angiotensin II infusion

Fig 1. Plots show plasma aldosterone concentration
in normotensive and normal-renin hypertensive
patients in basal low-salt state (left) and stimulated with 2
hours of upright posture (right). Note that low basal
aldosterone levels are common to both black and
white hypertensive patients, whereas the further stim-
ulus of upright posture uncovers a marked blunting of
aldosterone release among blacks. (Conversion factor
for aldosterone: ng/dL x 27.74 = pmol/L)

Fig 2. Plots show plasma aldosterone concentra-
tion in basal low-salt state (left) and during angio-
tensin II (Ang II) infusion (right). Although basal values
are similarly depressed in both black and white
hypertensive patients compared with normoten-
sive subjects, black patients demonstrate a
marked blunting of aldosterone release with the
further stimulus of angiotensin II infusion.
were not statistically significant. Previous studies have demonstrated normal aldosterone responses to Ang II, although sample sizes were small and the results were insufficient to replete the alleged dietary potassium deficiency in blacks. Alternatively, potassium absorption in blacks may be altered.

Subgroups of hypertensive patients were analyzed separately according to renin status. We found a 29% prevalence of low-renin hypertension among blacks and 11% among whites, consonant with earlier reports. Black low-renin hypertensive patients also tended to show a blunted adrenal response to both posture and Ang II, although sample sizes were small and the results were not statistically significant. Previous studies have demonstrated normal aldosterone responses to Ang II infusion among low-renin hypertensive patients, suggesting heightened sensitivity of the adrenal gland to Ang II stimulation. These studies, however, have been performed with patients on high sodium diets, which may account for the differing results.

In our study, blunted adrenal responses were common in black hypertensive patients, regardless of renin status. Among these patients, 72% had a rise in aldosterone of less than 555 pmol/L (<20 ng/dL) during Ang II infusion, nearly twice the percentage observed in whites (38%). Failure to enhance Ang II-mediated aldosterone release with restriction of salt intake is a salient feature of a group of white essential hypertensive patients—the "non-modulators." These salt-sensitive patients are also marked by a limited ability to handle sodium chloride, a renal blood flow rate that does not change with changes in salt intake, a fixed renal vascular response to Ang II, and abnormalities in the influence of saline or Ang II infusion on renin release. Moreover, most of these abnormalities are corrected by angiotensin converting enzyme inhibition. The limited ability to handle a sodium load in non-modulators and the correction of that abnormality by angiotensin converting enzyme inhibition have been attributed to abnormalities of the renal blood supply. Racial differences in renal vascular involvement in hypertension have been reported by multiple investigators, especially documentation that blacks excrete sodium loads more slowly than do whites, as in non-modulation, and have lower basal renal plasma flow. Whether the blunted adrenal response to Ang II in blacks is accompanied by other features of non-modulation, including blunted renal vascular responsiveness to Ang II during a high salt diet, and thus reflects a common pathogenesis remains to be ascertained.

Our study was designed to ensure that the two groups of hypertensive patients (blacks and whites) were well-matched for age, body mass index, and gender. Such a match was achieved. Similarly, the objective of matching black with white normotensive subjects was reached. Thus, any racial difference reported in this study cannot be attributed to differences in these demographic features. However, we were less successful in matching normotensive subjects with the hypertensive patients. The normotensive subjects were younger, leaner, and all male; one obvious physiological change with age is the increasing frequency of low-renin hypertension. Furthermore, the small size of the group of normotensive subjects studied, especially when viewed in light of the larger reports by Pratt et al. and Luft et al., indicates that conclusions about adrenal responsiveness in normotensive blacks await further study.

We have demonstrated a striking and frequent blunting of aldosterone release among black hypertensive patients, which becomes progressively more evident with increasing stimulation of the renin-angiotensin-aldosterone system. This physiological abnormality, dependent on the state of sodium balance, may indicate an underlying abnormality that predisposes blacks to hypertension, perhaps reflecting impaired renal sodium excretion and subsequent excessive volume retention.

Acknowledgments

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