

Aldosterone

Age-Related Blood Pressure Sensitivity to Aldosterone in Blacks and Whites

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Abstract—Aldosterone sensitivity, defined as the magnitude of the association of plasma aldosterone concentration with blood pressure (BP), seems to be a function of plasma volume. It increases as plasma renin activity decreases, and it is more significant in blacks but less so in whites. Age is a strong determinant of BP, and an increase in aldosterone sensitivity could contribute to the increase in BP. In the present study, we tested the hypothesis that aldosterone sensitivity increases with age. We used observational data collected from normotensive blacks and whites enrolled in a prospective cohort study. They were studied as children (248 blacks/357 whites) and again as young adults (74 blacks/125 whites) over an age range of 7 to 39 years. A varying-coefficient regression analysis was used to explore the influences of aldosterone on systolic BP. After controlling for body mass index, race, and sex, both plasma renin activity and plasma aldosterone concentration were lower in blacks, and their levels declined with age ($P<0.001$). In blacks, plasma aldosterone concentration decreased 0.25 ng/dL per year; in whites, plasma aldosterone concentration decreased 0.18 per year. Aldosterone's effect on BP, characterized by a smooth function of age, intensified as age increased, especially in blacks ($P<0.01$), suggesting an increased aldosterone sensitivity with age. In comparison to blacks, age-related changes in aldosterone sensitivity in whites were not statistically significant. These findings extend the rationale for targeting aldosterone in the treatment of hypertension, especially in blacks. (*Hypertension*. 2018;72:247-252. DOI: 10.1161/HYPERTENSIONAHA.118.11014.) • [Online Data Supplement](#)

Key Words: aldosterone ■ blood pressure ■ plasma volume ■ regression analysis ■ renin

Blood pressure (BP) increases with age. Indeed, most hypertension occurs later in life. Specific mechanisms for why BP changes as people become older remain poorly understood, although greater sodium retention with the secondary expansion of the plasma volume may be a principal underlying factor.¹ Primary hypersecretion of the sodium-retaining hormone, aldosterone, was once considered a rare cause of hypertension. We now know it accounts for $\approx 10\%$ of cases.^{2,3} Recently, it was shown that as individuals become older, they produce more aldosterone than can be explained by the level of plasma renin activity (PRA)—specifically, as age increased, aldosterone production took on characteristics consistent with having a certain level of autonomy.^{4,5} They depend less on regulation by the renin–angiotensin II system, as reflected in the level of PRA. There is, however, a tendency for the plasma aldosterone concentration (PAC) to decline with age, paralleling a decline in PRA.^{6,7} Although PAC may decrease, the capacity of aldosterone to influence BP should not be discounted because aldosterone sensitivity may come into play—a lesser amount of aldosterone is required to show an association with BP.

In the present study, we tested the hypothesis that aldosterone sensitivity increases with age. We used observational data collected from a longitudinally conducted cohort study,

first when subjects were children and again when some of the same subjects were young adults. Both blacks and whites were studied because ethnicity is known to affect aldosterone sensitivity.⁸ In this analysis, we characterized aldosterone sensitivity by the estimated magnitude of the BP-PAC association, obtained from a regression analysis. The findings could have relevance to the treatment of hypertension in older patients.

Methods

The data used in this analysis are available on request. Data access will be granted under the protection of a signed Data Use Agreement. We are happy to share computational code with interested parties. For all data and code requests, please contact the corresponding author.

Subjects and Study Design

The current analysis was based on data generated by a prospective cohort study started in 1986.^{9,10} The original study recruited healthy children between 5 and 17 years of age from schools in Indianapolis, IN for observations of BP. Children with renal or cardiac diseases, hypertension, diabetes mellitus, and individuals on BP-altering medications were excluded from participation. Enrolled subjects were assessed twice a year. Observations ended when the subjects completed high school. In 2008, we invited those who had participated in the childhood cohort to return for further evaluation as adults.⁸ The assessment protocol for the adult portion of the study was the

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same as for the child study. The adult study continued until 2013. The study protocols were approved by the Institutional Review Board of Indiana University. Informed consent was obtained from all adult subjects and from parents of children; assent was obtained from children as appropriate. We excluded from the current analysis individuals with a confirmed diagnosis of hypertension or those who were using BP-altering medications.

Measurements

We evaluated the subjects twice a year. They were seen between the hours of 07:00 and 11:00 in both the child and the adult studies. In the children, BP was measured in the right arm using a random zero sphygmomanometer (Hawksley & Sons, Lancing, West Sussex, United Kingdom), after subjects had been seated for 5 minutes. We used the first and the fifth Korotkoff sounds for systolic and diastolic BP. In the adult study, a similar protocol was followed with the exception that BP was measured using a mercury Baumanometer Standby Model (W.A. Baum Company, Copiague, New York). In both studies, BP was measured 3× two minutes apart, and the average of the last 2 readings was used in the analyses. For either study group, there was no restriction placed on a diet.

Subject's age was calculated from the date of birth. Body mass index (BMI) was calculated from height and weight at the time of assessment. Subject's race was self-reported and designation was confirmed against the HapMap phase 3 data.¹¹

Sample Processing and Assay Procedures

Subjects submitted overnight (≈12 hours) urine samples at all visits. Most subjects in the child study contributed only 1 blood sample. We collected blood from the adult subjects at all follow-up visits. Samples were processed at room temperature and stored at −80° C before assay. Specimens were then thawed and analyzed in batches within 3 weeks of collection. PRA was measured using a Clinical Assays GammaCoat radioimmunoassay kit (Baxter Healthcare, Cambridge, MA); plasma aldosterone and, after acid hydrolysis, urinary aldosterone concentrations were measured by radioimmunoassay with antiserum from Diagnostic Products Corporation (Los Angeles, CA). Serum and urinary sodium and potassium were measured using flame photometry.

Statistical Analysis

Baseline demographic characteristics of the study subjects in the child and adult studies were summarized and presented in a tabular form. Plasma and urine measurements were similarly summarized and presented. Continuous and categorical variables were analyzed with *t* and χ^2 tests, respectively. For skewed variables, we applied logarithmic transformation before making comparisons. To depict the age-related changes in BP, PRA, and PAC, we fitted semiparametric regression models to accommodate possible nonlinear patterns.¹² Estimated mean BP, PRA, and aldosterone levels at different ages were displayed as smooth functions of age. For BP, we adjusted effects of sex, race, and BMI as covariates. Finally, we used varying-coefficient models to describe the age-specific effects of PAC on systolic BP while controlling for the effects of sex, race, BMI, and PRA. The estimated BP effects of PAC were graphically presented as smooth functions of age. We quantified aldosterone sensitivity by the estimated age-specific aldosterone effects on BP. All analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>). *P* values <0.05 were considered as statistically significant.

Results

The current analysis was based on data contributed by 605 and 199 participants in the child and adult studies, respectively. Baseline characteristics of the child and adult study participants are described in Table 1. Blacks and whites, and males and females were tallied separately, and subject characteristics were compared using *t* tests. Differences

between male and female subjects within each race group were tested similarly (Table S1 in the [online-only Data Supplement](#)). Our analysis of the baseline data showed that (1) compared with white participants, black participants were slightly younger (*P* values ≤0.001) and on average had a greater BMI (*P* values <0.001); and (2) male subjects had higher systolic BP than females at the entry of both the child study and the adult study (*P* values <0.001). Figure S1 shows that systolic and diastolic BP increased with age in both blacks and whites; at any given age, levels of systolic and diastolic BP were not significantly different between the 2 race groups.

From the 605 subjects in the child study, we collected a total of 423 blood samples and 6373 urine samples. From the 199 subjects that participated in the adult study, we collected a total of 600 blood samples and 617 urine samples. Detailed summary statistics are presented in Table 2.

Data averaged over age showed that blacks had generally lower levels of PRA (black children, 3.09 ng/mL per hour versus white children, 3.30 ng/mL per hour; *P*=0.12; black adults, 1.04 ng/mL per hour versus white adults, 1.57 ng/mL per hour; *P*<0.0001) and PAC (9.10 ng/dL in black children versus 13.6 ng/dL in white children; *P*<0.0001; 5.1 ng/dL in black adults versus 9.5 ng/dL in white adults; *P*<0.0001). Urinary aldosterone excretion rates showed a similar race difference, with blacks having lower values. Males tended to have lower PAC and urinary aldosterone excretion rates than females, but the differences were not always statistically significant. Within race groups, men had lower PAC and urinary aldosterone excretion rates than women (*P*<0.03; Table S2).

To examine the age-related variations in PRA and PAC, we further estimated the mean PRA and PAC values at different ages. We present the estimated mean PRA levels in blacks and whites as functions of age in Figure 1A and 1B. PRA had age-related declines in blacks as well as in whites. In blacks, PRA decreased at a rate of 0.09 ng/mL per hour per year; in whites, PRA decreased at a rate of 0.08 ng/mL per hour per year. At any given age, blacks on average had lower PRA values (*P*<0.001). Similarly, PAC decreased with age in both race groups (Figure 1C and 1D). In blacks, PAC decreased at a rate of 0.18 ng/dL per year; in whites, PAC decreased at a rate of 0.25 ng/dL per year. At any given age, blacks had on average lower PAC levels (*P*=0.001). Aldosterone-to-renin ratio (ARR=PAC/PRA) increased with age in blacks and in whites (Figure 1E and 1F). Urinary aldosterone excretion showed similar decreasing patterns, but the rates of decline were not linear (Figure S2A and S2B). The more rapid decline in urinary aldosterone excretion during adolescence may be because of its expression as the ratio of urinary aldosterone and creatinine; the latter increased dramatically during puberty, presumably because of greater development of muscle mass (Figure S2C and S2D).

We conducted a varying-coefficient regression analysis to explore the influences of aldosterone on systolic and diastolic BP while controlling for the effects of BMI, race, sex, and PRA. The regression coefficient that represented aldosterone's effect on BP was characterized as a smooth function of age. The magnitudes of the estimated systolic

Table 1. Baseline Characteristics of Study Subjects When They Were Children and Then Again When Some of the Same Subjects Were Adults

Variables	Full Sample	White	Black	PValue	Male	Female	PValue
Characteristics of children at time of enrollment: mean (SD)							
N	605	357	248		306	299	
Age, y	14.61 (2.321)	14.94 (2.435)	14.14 (2.063)	<0.0001	14.65 (2.445)	14.58 (6.018)	0.7044
Systolic BP, mm Hg	108.69 (11.413)	108.48 (11.457)	108.98 (11.365)	0.5914	110.49 (12.414)	106.84 (10.493)	<0.0001
Diastolic BP, mm Hg	66.21 (10.385)	65.56 (10.645)	67.16 (9.944)	0.05953	65.93 (11.446)	66.50 (9.480)	0.5026
BMI, kg/m ²	23.05 (5.681)	22.13 (4.570)	24.35 (6.769)	<0.0001	22.90 (5.676)	23.20 (6.387)	0.5228
Characteristics of adults at time of re-enrollment: mean (SD)							
N	199	125	74		98	101	
Age, y	30.71 (4.152)	31.55 (4.058)	29.30 (3.944)	0.0002	31.04 (4.560)	30.40 (3.709)	0.2767
Systolic BP, mm Hg	114.43 (10.174)	114.49 (9.996)	114.34 (10.537)	0.9248	119.36 (8.960)	109.66 (8.962)	<0.0001
Diastolic BP, mm Hg	72.41 (9.317)	72.5 (8.993)	72.26 (9.901)	0.8627	74.61 (9.213)	70.27 (8.954)	0.0009
BMI, kg/m ²	28.67 (7.766)	27.27 (7.354)	31.03 (7.920)	0.0011	28.28 (5.894)	29.05 (9.242)	0.4852

BMI indicates body mass index; and BP, blood pressure.

BP-PAC association in blacks and whites are presented in Figure 2A and 2B. The figure clearly shows an intensified effect of aldosterone on systolic BP as age increases in blacks. No similar intensification was detected in whites. The estimated regression coefficient curves were significantly different ($P=0.023$), confirming a difference in aldosterone sensitivity between the 2 race groups. Similar effect patterns were observed for diastolic BP (Figure 2C and 2D).

Discussion

In the present study, observational data were collected from normotensive blacks and whites when they were children and again when they were young adults. We tested the hypothesis that aldosterone sensitivity, defined by the magnitude of the association between PAC and BP, increased with age in normotensive individuals. As stated in an earlier description of aldosterone sensitivity, it was the BP in black subjects that associated with the level of aldosterone—the BP in white

Table 2. Summary Statistics of Plasma and Urinary Measurements Averaged Over Age in Children and Adults

Variable	Full Sample	White	Black	PValue	Male	Female	PValue
Measurements from the child study: mean (SD)							
PRA, ng/mL per h*	3.24 (2.29)	3.30 (2.25)	3.09 (2.40)	0.1201	3.22 (2.10)	3.27 (2.49)	0.6292
PAC, ng/dL*	12.31 (8.520)	13.60 (8.94)	9.10 (6.34)	<0.0001	11.71 (7.53)	12.97 (9.46)	0.3554
Plasma K, mmol/L	4.22 (0.56)	4.20 (0.37)	4.28 (0.86)	0.3474	4.25 (0.49)	4.19 (0.62)	0.2611
Plasma Na, mmol/L	138.59 (3.36)	138.77 (3.31)	138.13 (3.46)	0.0833	138.75 (3.81)	138.41 (2.79)	0.2921
Urine creatinine, mg/dL	144.76 (66.98)	137.66 (62.47)	161.45 (73.90)	<0.0001	146.59 (68.34)	142.78 (65.42)	0.0231
Urine aldosterone, μ g/mg Cr*	5.40 (5.10)	5.92 (5.29)	4.18 (4.39)	<0.0001	5.42 (5.11)	5.37 (5.09)	0.5902
Urine K, mmol/g Cr*	30.60 (21.10)	32.03 (22.22)	27.25 (17.74)	<0.0001	31.97 (22.71)	29.11 (19.09)	<0.0001
Urine Na, mmol/g Cr*	122.00 (66.35)	122.95 (67.36)	119.76 (63.87)	0.367	123.21 (67.63)	120.68 (64.91)	0.2601
Measurements from the adult study: mean (SD)							
PRA, ng/mL per h*	1.36 (1.19)	1.57 (1.25)	1.04 (1.03)	<0.0001	1.26 (1.07)	1.42 (1.27)	0.1674
PAC, ng/dL*	7.72 (8.16)	9.50 (9.68)	5.10 (3.90)	<0.0001	6.04 (4.21)	8.89 (9.86)	0.0007
Plasma K, mmol/L	3.81 (0.27)	3.80 (0.28)	3.82 (0.26)	0.5481	3.86 (0.27)	3.77 (0.27)	0.00017
Plasma Na, mmol/L	138.49 (2.11)	138.60 (1.97)	138.33 (2.31)	0.1452	139.02 (2.17)	138.12 (2.00)	<0.0001
Urine creatinine, mg/dL	176.84 (86.40)	155.86 (74.35)	207.21 (93.49)	<0.0001	213.47 (86.00)	151.72 (77.31)	<0.0001
Urine aldosterone, μ g/mg Cr*	4.69 (5.060)	5.34 (5.809)	3.76 (3.524)	<0.0001	2.91 (2.095)	5.91 (6.043)	<0.0001
Urine K, mmol/mg Cr*	20.15 (13.03)	21.19 (15.19)	18.64 (8.85)	0.0080	18.63 (15.25)	21.19 (11.16)	<0.0001
Urine Na, mmol/mg Cr*	78.89 (42.44)	78.59 (42.79)	79.34 (42.00)	0.5958	66.91 (39.49)	87.11 (42.49)	<0.0001

PAC indicates plasma aldosterone concentration; and PRA, plasma renin activity.

*P values were obtained from 2 sample *t* tests based on logarithmic transformed data.

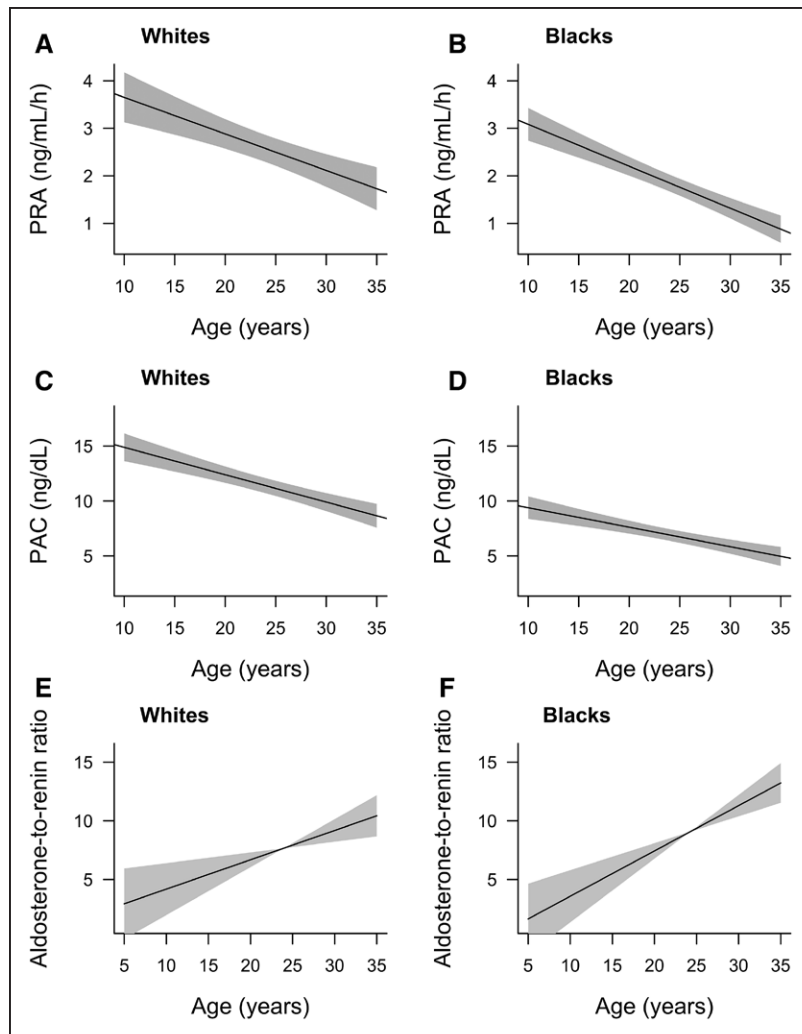


Figure 1. Age-related changes in plasma renin activity (PRA), plasma aldosterone concentration (PAC), and the aldosterone-to-renin ratio (ARR=PAC/PRA) in blacks and whites. Solid lines or curves represented the mean values of the estimated function. The shaded bands represented the 95% pointwise confidence intervals of the mean values at different ages. **A** and **B**, PRA decreased at a rate of 0.08 ng/mL per h per y in whites and 0.09 ng/mL per h per y in blacks; at any given age PRA was ≈ 0.44 ng/mL per h lower in blacks than in whites. **C** and **D**, PAC decreased at a rate of 0.25 ng/dL per y in whites and 0.18 ng/dL per y in blacks; at any given age, PAC in blacks on average was 5.2 ng/dL lower than whites. **E** and **F**, Values of ARR in blacks and in whites increased with age; the rate of increase was greater in blacks.

subjects was weakly associated with PAC if it was associated at all.⁸ The current analysis further details age-related variations in BP, PRA, PAC, and in the PAC–BP relationship. Our data showed a significantly strengthened PAC–BP association as black subjects grew older, even though subjects were still quite young. In whites, PAC showed a more attenuated pattern of influence on BP, one that may have increased slightly but fell short of statistical significance. Interestingly, the ARR increased with age in both race groups, but the rate of increase was greater in blacks. Although one may contemplate the merits and shortcomings of using ARR to gauge aldosterone sensitivity, the increase in ARR with age clearly reinforces the impression that mineralocorticoid receptor activity increases as one grows older, especially in blacks.

We can only speculate on a mechanism for the age-related increase in aldosterone sensitivity. There is a reciprocal relationship between aldosterone sensitivity and PRA—as PRA decreases, aldosterone sensitivity increases. A preexisting state of increased sodium retention reflected in the larger volume may not accommodate additional sodium uptake mediated by aldosterone. A pressure natriuretic response to restore sodium balance would account for the higher BP. This, of course, does not preclude the participation of other renal mechanisms that might result in enhanced BP effect of aldosterone.¹³

Other low-renin, aldosterone-associated conditions may overlap with aldosterone sensitivity. Autonomous aldosterone production in individuals without obvious primary aldosteronism showed a strong relation to age.³ These patients may have adrenal cell clusters as sites for increased aldosterone synthesis.^{4,5} Patients referred to as having subclinical primary aldosteronism might also synergize with aldosterone sensitivity.¹⁴ Finally, it should be noted that in the present study, mean potassium concentrations were lower in the adults than in the children (3.82 versus 4.22 mmol/L). This difference is consistent with a greater plasma volume in the adults.¹⁵

Probably the strongest experimental evidence in support of volume-regulated aldosterone sensitivity comes from a study of normotensive blacks and whites, where administration of the synthetic mineralocorticoid 9- α fludrocortisone (0.2 mg per day for 2 weeks) increased BP in black subjects but not in white subjects.⁸ Both PRA and PAC decreased in whites but not in blacks, consistent with a capacity by whites to seemingly buffer a mineralocorticoid-mediated response.

Although what precisely underlies the age-dependent reliance of BP on PAC is unclear, a higher PAC per se is an unlikely explanation because it actually decreased with age. A heightened sensitivity in blacks probably stems from an age-associated plasma volume expansion,⁸ as suggested by

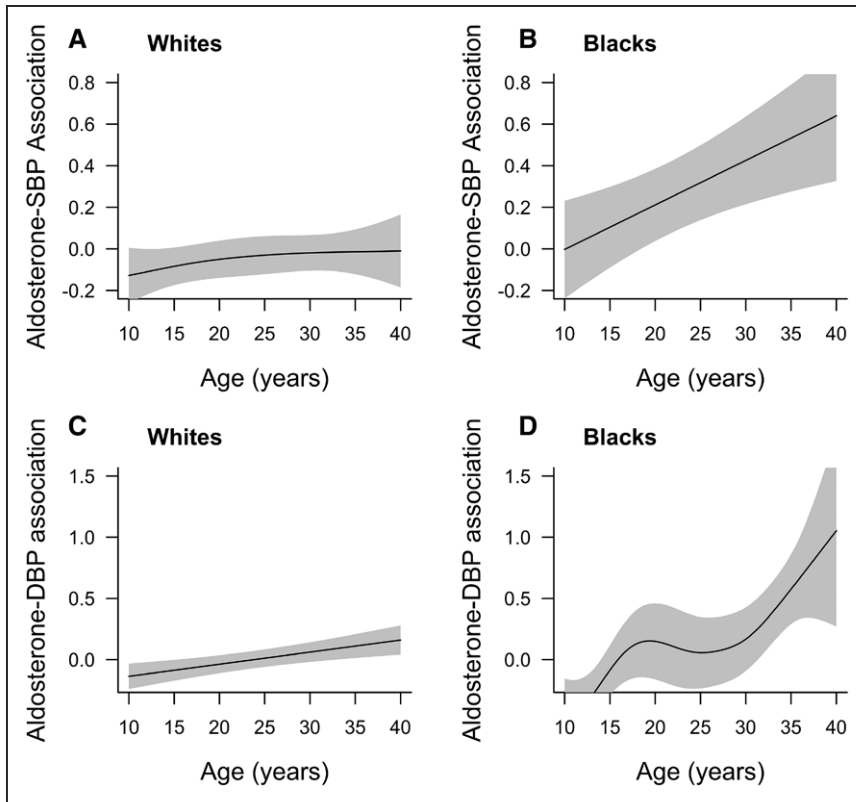


Figure 2. Age-specific estimates of the aldosterone-systolic blood pressure (SBP) association in blacks and whites. **A and B,** Magnitudes of the estimated aldosterone-SBP association significantly increased with age in blacks ($P<0.01$) but not in whites. The 2 estimated regression coefficient curves were significantly different per bootstrap test ($P=0.023$). **C and D,** Age-specific estimates of the aldosterone-diastolic BP (DBP) in whites and in blacks. Shaded regions represent 95% pointwise confidence intervals of the mean curves.

the decreasing PRA and increasing ARR with age in blacks. The consistency of the observed time trends suggests that aldosterone sensitivity may increase with age in all race groups but may manifest earlier in individuals of African ancestry. Finally, age-related molecular variations in the mineralocorticoid receptor such as enhancement of ligand binding or postreceptor activation could also contribute to our findings.^{16–18}

The current study utilized subjects who were young (7–39 years of age) and healthy. To what extent our findings can be extrapolated to older and hypertensive individuals will require further study, although it is difficult to imagine that the time trends of PRA, PAC, and BP that we observed in the current study would reverse themselves in older individuals. Among other things, findings made from healthy individuals under conditions free of the influences of antihypertensive agents are likely to more accurately reflect the true and unmanipulated associations between aldosterone and BP.

Observations made in the present study suggest that antagonists of aldosterone action, drugs that block the mineralocorticoid receptor or drugs that inhibit directly the epithelial sodium channel, could prove useful for older hypertensive patients, particularly blacks. We note that published interventional studies of mineralocorticoid receptor antagonists, such as spironolactone, or direct inhibitors of epithelial Na channels, such as amiloride, were effective in reducing BP in resistant and low-renin hypertension.^{19–21} Recent recommendations for a lower goal BP for older patients has made treatment even more challenging,^{22,23} and new pharmacological approaches need to be considered. Candidate drugs should include those that mitigate the actions of aldosterone.

Perspectives

High blood pressure becomes more common as people get older. We show in the present study that sensitivity to a potent sodium-retaining hormone, aldosterone, may be an important contributor to age-associated hypertension. This may be more true of blacks than whites. Drugs that interfere with aldosterone's actions, such as spironolactone, may be particularly effective for the treatment of hypertension.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Aldosterone sensitivity, the magnitude of the association of plasma aldosterone concentration with blood pressure, was shown to increase with age. There is a less than fully appreciated role for aldosterone in development of hypertension as individuals become older.
- A normal plasma aldosterone concentration affects blood pressure that might otherwise be anticipated, particularly in the elderly patient and if the patient is black.

What Is Relevant?

- The role played by aldosterone in establishing a level of blood pressure and risk for hypertension continues to expand. Although the

current study used data collected from nonhypertensive subjects, it nevertheless suggests that in choosing antihypertensive drug therapy for older patients, the drug's ability to inhibit aldosterone's actions be considered.

Summary

Aldosterone's effect on blood pressure intensified as age increased. In comparison to whites, age-related changes in aldosterone sensitivity in blacks were striking. The findings extend the usefulness of targeting aldosterone in the treatment of hypertension and more so in blacks than in whites.