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Aldosterone Contributes to Elevated Left Ventricular Mass in Black Boys

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Abstract

Background—Left Ventricular Hypertrophy (LVH) poses a great risk of cardiovascular morbidity and mortality in adults and may pose a serious risk in children. Adult studies have shown Renin Angiotensin Aldosterone System (RAAS) levels are directly correlated with left ventricular mass index (LVMI). This purpose of this study is to explore race and sex-related effects of the RAAS on LVMI in adolescents.

Methods—Data was collected from a sample of 89 blacks (44 girls, 45 boys) and 102 whites (40 girls, 62 boys) ages 15–19. Data collected included, sex, age, body mass index (BMI), LVMI, baseline blood pressure, and levels of aldosterone and angiotensin II.

Results—In black males, increased aldosterone levels were correlated with decreased sodium excretion ($r=-0.336$, $p=0.024$), increased blood pressure ($r=0.358$, $p=0.016$), and increased LVMI ($r=0.342$, $p=0.022$). In black females, increased aldosterone levels correlated with increased baseline blood pressure ($r=0.356$, $p=0.018$). In white males, increased aldosterone was correlated decreased sodium excretion ($r=-0.391$, $p=0.002$). In white females, aldosterone levels correlated with increased baseline blood pressure ($r=0.323$, $p=0.042$) and decreased sodium excretion ($r=-0.342$, $p=0.031$).

Conclusions—The results suggest the following model in black males: increased aldosterone leads to increased sodium retention, causing a volume-mediated increase in blood pressure; increased blood pressure results in increased left ventricular mass and eventually LVH.

Keywords

hypertension; renin; angiotensin; aldosterone; left ventricular hypertrophy; adolescents

Introduction

It is well-documented that cardiovascular disease begins in youth.[1–3] Unfortunately, the prevalence of cardiovascular disease is increasing among this population,[4–7] which will also have consequences for the future adult population. Furthermore, studies by our

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group[8–12] and others[3,13–16] have demonstrated that African-American youth compared to Caucasian youth have a faster progression in the development of cardiovascular disease, [8–10,12] particularly in boys.

Aldosterone's role in cardiovascular disease has previously been studied. Aldosterone is expected to decrease sodium excretion and increase blood pressure, as previously noted in adult populations.[17] One pediatric study suggested the aldosterone-renin ratio may be an early predictor of target organ damage in children.[18] Our study aims to expand on this finding. The purpose of this study was to determine if racial and gender differences of aldosterone concentration contribute to these differences of disease progression across race and sex. To do this, we examined the effects of race and sex on aldosterone concentration, and the effects of race, sex, and aldosterone concentration on blood pressure, left ventricular mass, and urinary sodium excretion in a large sample of healthy adolescents. This study gives comprehensive results as it includes both black and white adolescents for comparison. Such an understanding of race and sex-related variation in children is beneficial in clinical practice. Ultimately, a better understanding of aldosterone's role in blood pressure regulation and left ventricular mass size may contribute to improved treatment of hypertension and left ventricular hypertrophy in adolescents.

Methods

Subjects

The protocol was approved by the Human Assurance Committee of the Medical College of Georgia. Written informed parental consent and subject assent was obtained prior to testing. The 191 unrelated subjects were healthy and on no over-the-counter or prescription medicines, except acne medicines. They were recruited from local schools by word of mouth. Left ventricular mass index (LVMI), plasma aldosterone and angiotensin II levels, urinary sodium excretion, and baseline systolic blood pressure (baseline SBP) were obtained.

Protocol and Procedures

The protocol consisted of a screening phase and a testing phase, held within one month of each other. During the screening phase, consent was obtained. Prior to the testing phase, subjects were placed on a diet of 4000 ± 200 mg of sodium and 2600 ± 200 mg of potassium per day for 3 days; overnight urine collections were used to determine compliance with the diet protocol.[19] Urinary sodium excretion per minute was measured, and values between 3.5 and 7.5 mEq/min were considered compliant. Only compliant cases were used in the study.

On the morning of testing, subjects were given breakfast then moved to the testing room. Subjects were relaxed and seated during the protocol. Ambulation was allowed only for the purpose of collecting urine samples. Measurements were recorded before, during, and after an hour of rest. The subjects' blood pressure and heart rates were measured by a Dinamap blood pressure monitor at 15-minute intervals and averaged across the hour to calculate 'baseline' blood pressures and heart rates. Urine and blood samples were collected at the end of the hour for analysis of angiotensin II, aldosterone, and urinary sodium excretion ($U_{Na}V$, measured in milliequivalents per hour). Laboratory methods have been previously described [19]. Briefly, plasma angiotensin II was measured by American Laboratories Products Company RIA kit 001rka22. Plasma aldosterone was measured by Diagnostic Systems Laboratories RIA kit 8600. Left ventricular mass index ($LVM/ht^{2.7}$) was obtained by echocardiography, using procedures described previously.[20,21] These procedures were part of a larger protocol. Echocardiograms were read independently.

Data Analysis

Analysis included one-hour angiotensin II and aldosterone, urinary sodium excretion, left ventricular mass index, and baseline systolic blood pressure. The distribution of aldosterone and angiotensin II was skewed; therefore, analysis was performed using the natural log transformation

Statistics

The data were analyzed with SPSS 17.0 (IBM, Chicago, IL, USA). We used analysis of variance (ANOVA) tests and a $p < 0.05$ threshold for statistical significance, adjusted for multiple comparisons. We determined the effect of sex and race on body mass index, systolic blood pressure, diastolic blood pressure, heart rate, left ventricular mass index, urinary sodium excretion, log transformed serum aldosterone concentration, and log transformed serum angiotensin II concentration. Pearson correlation coefficients were used to examine relationships between the log transformed serum aldosterone concentration and three variables: urinary sodium excretion, left ventricular mass index, and systolic blood pressure. A $p < 0.05$ was considered significant.

Results

Subjects

Table 1 shows the mean values and ranges for each race and sex group. Analysis of variance test indicated that sex was a significant factor for baseline systolic blood pressure ($p < 0.001$), baseline heart rate ($p < 0.001$), left ventricular mass index ($p < 0.005$), log transformed aldosterone concentration ($p < 0.001$), and log transformed angiotensin II concentration ($p = 0.0043$). Race was a significant factor for body mass index ($p = 0.003$), baseline diastolic blood pressure ($p < 0.001$) and log transformed serum aldosterone concentration ($p < 0.001$). No statistically significant sex-race interaction occurred. White subjects had higher serum aldosterone levels (Table 1).

Of note, 16 of the subjects were obese. This group included 9 black girls, 4 black boys, 1 white girl, and 2 white boys. No significant correlations with aldosterone were found within this group as this was a small cohort.

In black boys, log transformed aldosterone was positively correlated with baseline systolic blood pressure (SBP) ($r: 0.358$, $p = 0.016$, Figure 1a) and LVMI ($r: 0.342$, $p = 0.022$, Figure 1b). Log transformed aldosterone levels were correlated with baseline SBP in black girls ($r: 0.356$, $p = 0.018$, Table 2) and white girls ($r: 0.323$, $p = 0.042$, Table 2), but no such correlation was found in white boys. Log transformed aldosterone was inversely correlated with urinary sodium excretion; this relationship existed in black boys ($r: -0.336$, $p = 0.024$, Table 2), white boys ($r: -0.391$, $p = 0.002$, Table 2) and white girls ($r: -0.342$, $p = 0.031$, Table 2). No such relationship was seen in black girls. In all groups, no significant relationships were seen with log transformed angiotensin II levels. Correlations are depicted in Table 2. Our results remained significant when we controlled for BMI.

To test our hypothesis, we began by looking for a race-by-sex interaction. The interaction was present ($\beta = -0.322$, $p = 0.031$) such that black boys had the lowest mean $\ln[\text{aldosterone}]$ levels, while white girls had the highest.

Discussion

This pattern of correlation coefficients suggests that there may be race and sex dependent effects of aldosterone on urinary sodium excretion, systolic blood pressure, and left

ventricular mass index. Our results show that aldosterone is related to urinary sodium excretion, systolic blood pressure (SBP), and left ventricular mass index (LVMI) in young black boys only. The mechanism can be depicted by the model in Figure 2: increased aldosterone leads to increased sodium retention, causing a volume-mediated increase in blood pressure; increased blood pressure results in increased left ventricular mass and eventually left ventricular hypertrophy.

White boys only showed aldosterone levels that were negatively correlated with sodium excretion. These results seem to show that white boys do not display an aldosterone-dependent volume-mediated increase in blood pressure. Additionally, our results remained significant even when we controlled for BMI. White subjects had higher serum aldosterone levels than black subjects (Table 1). This difference was also found in a previous study of black and white adolescents [18].

Prior studies also suggest that there may be race and sex dependent differences involving hypertension and aldosterone. A study of hypertensive middle-aged subjects in London demonstrated that black subjects had significantly higher aldosterone levels than white subjects despite low renin levels [22]. One study of hypertensive and normotensive adults found plasma aldosterone levels and plasma aldosterone-renin ratios correlated with blood pressure in African Americans but not white French Canadians.[23] This study suggests that excess aldosterone, reflected by high plasma aldosterone to renin ratios, contributes to hypertension in blacks. Additionally, a study of black adults found plasma aldosterone was higher in hypertensive subjects than normotensive subjects, suggesting that hypertension may be related to aldosterone-mediated sodium retention.[17]

The correlation between aldosterone levels and LVM in black boys is similar to previous findings. In a study of a pediatric population consisting predominantly of African-American boys, Li et al found a significant association between the aldosterone-renin ratio and LVM index. These results suggest the aldosterone-renin ratio may be an early predictor of target organ damage in children.[18] Additionally, aldosterone levels are higher in men than in premenopausal women, likely due to the anti-aldosterone effects of estrogen and progesterone.[24] Our study is unique because it shows aldosterone is correlated with LVMI in black boys only. Additionally, our study demonstrated the relationship was significant at each step of the Renin-Angiotensin-Aldosterone System (Figure 2).

Such a model suggests targeting aldosterone when treating hypertension and LVH in young black boys. Pharmacological treatment studies in children are sparse, but adult studies yielded positive results. One hypertension treatment study of a predominately black adult population demonstrated that eplerenone, an aldosterone blocker, was more effective than losartan, an angiotensin II receptor antagonist.[25] Similarly, Pitt et al[26] showed that angiotensin converting enzyme (ACE) inhibitors are not effective in thoroughly suppressing aldosterone. They suggest that other mechanisms, such as serum potassium levels, are more powerful aldosterone regulators.[26] Aldosterone blockers have generally been avoided in clinical practice due to side effects such as gynecomastia. However, eplerenone is a more selective aldosterone antagonist. It was shown to produce a much lower incidence of side effects when compared to the older aldosterone blocker spironolactone.[25,26] One adult study showed eplerenone was effective in treating resistant hypertension, with clinical systolic blood pressure control rates as high as 60% [26].

Limitations

Our study was limited to 15–19 year olds. Although our study had the advantage of demonstrating relationships in this age group, we are unable to generalize our findings to the entire pediatric population. We used spot sodium excretion; a 24-hour collection would have

produced more accurate results. Additionally, we measured casual blood pressure using an automated device rather than using 24-hour ambulatory monitoring. Our study population only included healthy individuals. However, these findings in healthy adolescents translate to adults.[27] Further analysis of hypertensive adolescents is indicated for future studies to test our hypothesis. Future studies could address adolescents with a family history of hypertension as well. Our highest correlation coefficient was 0.391, implying that aldosterone concentration accounts for only a small part of the variation that occurs in sodium excretion, blood pressure, and left ventricular mass.

Conclusion

Our results support the hypothesis that aldosterone contributes to race and sex related variations in urinary sodium excretion, systolic blood pressure, and left ventricular mass in adolescents. Additionally, aldosterone is related to urinary sodium excretion, systolic blood pressure, and left ventricular mass index in young black boys only. We believe these results reveal a model for aldosterone-mediated hypertension and left ventricular hypertrophy and may be an important tool in treating such disorders in young black boys.

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List of Common Abbreviations

BMI	body mass index
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMi	left ventricular mass index
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure

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Figure 1.

Figure 1a. Relationship between systolic blood pressure (mm Hg) and log of aldosterone (ln[Aldosterone], pg/ml).

Figure 1b. Relationship between left ventricular mass index (g/m²) and log of aldosterone (ln[Aldosterone], pg/ml).

Figure 2.
Effects of aldosterone on the cardiovascular system of young black boys.

Table 1

Subject characteristics

Variable	Black Boys Mean (range)	Black Girls Mean (range)	White Boys Mean (range)	White Girls Mean (range)
Number of subjects	45	44	62	40
Age, yr	16 (15–18)	16 (15–19)	17 (15–19)	17 (15–19)
Weight, kg	74 (50–123)	69 (49–123)	70 (44–124)	60 (43–95)
Height, cm	175 (163–185)	163 (154–175)	176 (155–190)	163 (157–169)
BMI, kg/m ²	24 (17–42)	26 (17–45)	22 (16–37)	22 (17–31)
Baseline HR, bpm	68 (54–87)	76 (59–102)	64 (50–84)	76 (61–89)
Baseline SBP, mmHg	115 (93–135)	108 (92–137)	113 (96–143)	104 (93–116)
Baseline DBP, mmHg	59 (49–75)	59 (48–75)	54 (45–63)	57 (45–69)
LVM/ ht ^{2.7} m	33 (22–60)	31 (18–56)	32 (20–44)	28 (21–40)
UNaV, mEq/hr	15 (2–39)	12 (4–29)	13 (3–40)	10 (4–19)
ln[Aldosterone], pg/ml	4.5 (3.7–5.6)	4.7 (3.5–6.0)	4.6 (2.4–6.0)	5.2 (4.0–6.2)
ln[Ang II], pg/ml	2.5 (1.1–4.6)	3.0 (1.6–4.3)	2.7 (1.4–4.4)	2.8 (1.1–3.8)

BMI-body mass index; HR-Heart rate; SBP-systolic blood pressure; DBP-diastolic blood pressure; LVM-Left ventricular mass; UNaV- urinary sodium excretion; ln[Aldosterone]-natural log of aldosterone; ln[Ang II]-natural log of angiotensin II; UNaV – urinary sodium excretion

Table 2

Correlations of urinary sodium excretion, systolic blood pressure, and left ventricular mass index with serum log aldosterone concentration, pg/mL*

	Black Boys	Black Girls	White Boys	White Girls
UNaV, mEq/hr	r: -0.336 [†]	r: -0.041	r: -0.391 [†]	r: -0.342 [†]
SBP, mm Hg	r: 0.358 [†]	r: 0.356 [†]	r: -0.013	r: 0.323 [†]
LVMI, g/m ²	r: 0.342 [†]	r: -0.181	r: -0.007	r: 0.166

UNaV- urinary sodium excretion; SBP-systolic blood pressure; LVMI-Left ventricular mass index

[†]
p<0.05