Aldosterone & Cardiometabolic Risk Factors

Abnormal Aldosterone Physiology and Cardiometabolic Risk Factors

Anand Vaidya,* Patricia C. Underwood,* Paul N. Hopkins, Xavier Jeunemaitre, Claudio Ferri, Gordon H. Williams, Gail K. Adler

Abstract—Abnormal aldosterone physiology has been implicated in the pathogenesis of cardiometabolic diseases. Single aldosterone measurements capture only a limited range of aldosterone physiology. New methods of characterizing aldosterone physiology may provide a more comprehensive understanding of its relationship with cardiometabolic disease. We evaluated whether novel indices of aldosterone responses to dietary sodium modulation, the sodium-modulated aldosterone suppression-stimulation index (SASSI for serum and SAUSSI for urine), could predict cardiometabolic risk factors. We performed cross-sectional analyses on 539 subjects studied on liberal and restricted sodium diets with serum and urinary aldosterone measurements. SASSI and SAUSSI were calculated as the ratio of aldosterone on liberal (maximally suppressed aldosterone) to the aldosterone on restricted (stimulated aldosterone) diets and associated with risk factors using adjusted regression models. Cardiometabolic risk factors associated with either impaired suppression of aldosterone on liberal diet, or impaired stimulation on restricted diet, or both; in all of these individual cases, these risk factors associated with higher SASSI or SAUSSI. In the context of abnormalities that constitute the metabolic syndrome, there was a strong positive association between the number of metabolic syndrome components (0–4) and both SASSI and SAUSSI (P<0.0001) that was independent of known aldosterone secretagogues (angiotensin II, corticotropin, potassium). SASSI and SAUSSI exhibited a high sensitivity in detecting normal individuals with zero metabolic syndrome components (86% for SASSI and 83% for SAUSSI). Assessing the physiological range of aldosterone responses may provide greater insights into adrenal pathophysiology. Dysregulated aldosterone physiology may contribute to, or result from, early cardiometabolic abnormalities. (Hypertension. 2013;61:886-893.) ● Online Data Supplement

Key Words: adrenal ■ aldosterone ■ metabolic syndrome ■ physiology ■ renin

The renin–angiotensin–aldosterone system (RAAS) is a dynamic hormonal system. The manner in which the RAAS responds to physiological provocations, such as dietary sodium modulation, characterizes RAAS physiology and abnormalities in RAAS regulation may be associated with cardiometabolic diseases. This is highlighted in the literature that links aldosterone, using single cross-sectional measurements, with clinical outcomes and adverse cardiometabolic profiles.1–10 Improving the understanding of aldosterone dysregulation may provide insights into new avenues for the treatment and prevention of pathological conditions associated with altered adrenal physiology.

Aldosterone dysregulation has been associated with cardiometabolic risk factors, and individual components of the metabolic syndrome (MetS) associate with higher aldosterone concentrations in human studies.6–13 These studies used single aldosterone measures as the predictor, rather than evaluating the dynamic physiology that regulates aldosterone responses and actions and has been previously correlated with cardiometabolic pathophysiology.14–18 For example, high-sodium dietary interventions maximally suppress adrenal aldosterone secretion; the inability to suppress aldosterone in this setting has been associated with insulin resistance, dyslipidemia, obesity, and diabetes mellitus.7,14,19 In contrast, induction of a very restricted (RES) sodium balance, or the infusion of exogenous angiotensin II (AngII), stimulates adrenal aldosterone secretion; a blunted stimulation of aldosterone in these settings has also been associated with similar cardiometabolic abnormalities.14–16,18,20,21 Therefore, we speculated that the integration of aldosterone suppression and stimulation would provide an improved representation of aldosterone physiology in disease states that could offer new insights in the pathogenesis and treatment of cardiometabolic derangements.

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We developed a novel index to reflect physiological aldosterone responses to dietary sodium manipulation. This index integrates aldosterone physiology via a ratio of aldosterone levels on a liberal sodium (LIB) diet:levels on a RES sodium diet. In this manner, this integrated index captures physiological abnormalities in aldosterone suppression, aldosterone stimulation, and also when both of these responses are mildly or severely abnormal. For serum measures, we define the index as the sodium-modulated aldosterone suppression-to-stimulation index (SASSI), and for urinary aldosterone measures we define the index as the sodium-modulated aldosterone urinary suppression-to-stimulation index (SAUSSI). We hypothesized that abnormal aldosterone responses to dietary salt interventions (high SASSI or high SAUSSI) would associate with individual cardiometabolic risk factors and with aggregate constellations of cardiometabolic risk, such as the MetS. These findings could better define the development of abnormal aldosterone physiology with progressive cardiometabolic abnormalities and provide mechanistic insights for future intervention studies.

Research Design and Methods

Study Population and Protocol

Study Population

A cross-sectional analysis of participants studied in the International Hypertensive Pathotype (HyperPATH) protocol, a data set consisting of abnormal aldosterone physiology with progressive cardiometabolic abnormalities in aldosterone physiology via a ratio of aldosterone levels on a liberal sodium (LIB) diet:levels on a RES sodium diet. In this manner, this integrated index captures physiological abnormalities in aldosterone suppression, aldosterone stimulation, and also when both of these responses are mildly or severely abnormal. For serum measures, we define the index as the sodium-modulated aldosterone suppression-to-stimulation index (SASSI), and for urinary aldosterone measures we define the index as the sodium-modulated aldosterone urinary suppression-to-stimulation index (SAUSSI). We hypothesized that abnormal aldosterone responses to dietary salt interventions (high SASSI or high SAUSSI) would associate with individual cardiometabolic risk factors and with aggregate constellations of cardiometabolic risk, such as the MetS. These findings could better define the development of abnormal aldosterone physiology with progressive cardiometabolic abnormalities and provide mechanistic insights for future intervention studies.

Study Protocol

Details of this protocol have been described previously.20 In brief, to control the influence of medications on components of the RAAS, all angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists were discontinued for 3 months before study, and β-blockers, calcium-channel blockers, and diuretics were discontinued for at least 2 weeks before the study. If necessary, participants were briefly given amlodipine for BP control; however, this was discontinued 2 weeks before the start of the study procedures.

Participants completed 2 diets for 5 to 7 days each: LIB sodium (200 mmol/d) and RES sodium (10 mmol/d) with each diet also containing 100 mmol/d potassium and 20 mmol/d calcium. On completion of each diet phase, participants were admitted overnight to the clinical research center. Sodium balance was confirmed by 24-hour urine collection. For this analysis, only subjects with verified urinary sodium of ≥150 mmol sodium/d on LIB diet and ≤40 mmol sodium/d on RES diet were included. Baseline measurements for insulin, glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein triglycerides, plasma renin activity (PRA), serum aldosterone, and BP were obtained in the morning after overnight supine rest, using standardized and validated methods as previously described.18-25 After baseline blood draws were collected on RES diet, an infusion of AngII (Bachem AG, Bubendorf, Switzerland) (3 ng/kg per min for 60 minutes) was administered as previously described,22 and measurements for serum aldosterone and PRA were repeated at the end of the infusion. Insulin resistance was measured using the homeostatic model assessment as previously described.25

In the morning of the fifth day of the LIB diet, a portion of the nondiabetic participants reported to the ambulatory clinical research center and received a 75 g oral glucose tolerance test. The oral glucose tolerance test was conducted as previously described.27,28

Development of the SASSI and SAUSSI

We used aldosterone and PRA measurements from our study protocols to develop integrated indices reflecting dynamic RAAS physiology that we could then use in the assessment of cardiometabolic risk factors. Among the many methods to measure the RAAS (Table S1 in the online-only Data Supplement), we used only those that were obtained during the aforementioned control of diet, posture, and interfering medications. The ratio of single supine serum aldosterone measurements on LIB and RES diets was used to calculate the SASSI (ratio of dietary sodium-suppressed aldosterone-dietary sodium-stimulated aldosterone) (Figure 1). The ratio of 24-hour urinary aldosterone excretion on both LIB and RES diets was used to calculate the SAUSSI (ratio of dietary sodium-suppressed urinary aldosterone excretion:dietary sodium-stimulated urinary aldosterone excretion). The ratio of the supine serum aldosterone on LIB diet:the serum aldosterone after an infusion of AngII on RES diet was termed the SASSI-II, and used as an index of the maximally dietary sodium-suppressed aldosterone to the AngII-stimulated aldosterone (Figure 1). The SASSI-II was developed to provide more information than the SASSI or SAUSSI might alone because AngII stimulation on RES diet provides a measure of adrenal aldosterone stimulation that is independent of other endogenous RAAS components (AngII and PRA). Thus, although the physiological responses of PRA, AngII, and aldosterone are expected to be examination with a medical history, physical examination, ECG, and laboratory evaluation. Participants with known or suspected secondary hypertension, coronary artery disease, stroke, overt renal insufficiency (serum creatinine >1.5 mg/dL), psychiatric illness, current oral contraceptive use, current tobacco/illicit drug use, or moderate alcohol use were excluded. Participants with abnormal electrolyte or thyroid/liver function tests or electrocardiographic evidence of heart block, ischemia, or previous coronary events at the screening examination were excluded. All participants were between the ages of 18 and 65 years. Race was obtained via participant self-report. The protocol was approved by the institutional review boards of each site, and informed consent was obtained before participant enrollment.

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A cross-sectional analysis of participants studied in the International Hypertensive Pathotype (HyperPATH) protocol, a data set consisting of individuals who underwent rigorous profiling of the RAAS under controlled conditions, was conducted. Five centers contributed to this data set: Brigham and Women’s Hospital (Boston, MA); University of Utah Medical Center (Salt Lake City, UT); Hospital Broussais (Paris, France); University of Rome (Rome Italy); and Vanderbilt University (Nashville, TN). For this analysis, we included individuals who successfully completed all study procedures and had complete data for all 4 components of the MetS according to the World Health Organization criteria22 (hypertension, insulin resistance [fasting glucose and insulin], body mass index [BMI], and hyperlipidemia [high-density lipoprotein and triglyceride levels]). Although the MetS is heterogeneous and not inclusive of all risk factors (for example, age, race, and sex are not a part of the MetS definition), we used the MetS as a model of a predefined, and well-known, compounded cardiometabolic risk state. The HyperPATH cohort characterized hypertension as a seated diastolic blood pressure (BP) of ≥100 mm Hg of antihypertensive medications, ≥90 mm Hg taking ≥1 medication, or treatment with ≥2 medications. Type 2 diabetes mellitus was defined per American Diabetes Association criteria as follows22: fasting blood glucose ≥126 mg/dL, random blood glucose ≥140 mg/dL, HgA1c ≥6.5%, 2-hour oral glucose tolerance test blood glucose ≥200 mg/dL, or a previous physician confirmed diabetes mellitus diagnosis.22 A participant was considered to have the MetS if they had type 2 diabetes, obesity, hypertension, hyperlipidemia, and hyperglycemia. Although other results from the HyperPATH cohort have been reported previously,14-16,20 the present analyses are original. All inclusion and exclusion criteria for the HyperPATH protocol are described elsewhere.20 In brief, all participants received a screening examination with a medical history, physical examination, ECG, and laboratory evaluation. Participants with known or suspected secondary hypertension, coronary artery disease, stroke, overt renal insufficiency (serum creatinine >1.5 mg/dL), psychiatric illness, current oral contraceptive use, current tobacco/illicit drug use, or moderate alcohol use were excluded. Participants with abnormal electrolyte or thyroid/liver function tests or electrocardiographic evidence of heart block, ischemia, or previous coronary events at the screening examination were excluded. All participants were between the ages of 18 and 65 years. Race was obtained via participant self-report. The protocol was approved by the institutional review boards of each site, and informed consent was obtained before participant enrollment.

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Statistical Analyses

Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Population characteristics for individuals with and without MetS were compared using a Student t test. A χ² analysis was used for comparison of categorical variables. Data are represented as means±SD. The main analyses for this study included univariate and multivariate regression analyses to analyze the relationship between individual cardiometabolic risk factors and measures of aldosterone; the relationship between these aldosterone measurements and increasing components of the MetS (0–4); and the odds of having MetS (yes/no) using linear and logistic regression adjusted for age, sex, and race.29–31 Sensitivity and specificity analyses were conducted to evaluate whether physiological aldosterone measurements could distinguish healthy individuals from those with MetS compared with those without MetS. In contrast, a nonsignificant trend toward lower serum and urinary aldosterone levels was observed during RES diet conditions.

SASSI and SAUSSI as Predictors of Individual and Aggregate Cardiometabolic Risk

We evaluated the correlation between aldosterone measurements and individual cardiometabolic risk factors. Serum
Aldosterone on LIB diet was positively correlated with BP, BMI, and lipid parameters, suggesting that the lack of aldosterone suppressibility is a predictor of these risk factors (Table 2). In contrast, serum aldosterone on RES diet was inversely associated with age and BMI, suggesting an inability to appropriately stimulate aldosterone as a predictor for these risk factors. When these aldosterone measures were integrated as the SASSI, this single index displayed strong positive associations with age, male sex, BP, and BMI, thereby combining the predictive power of single aldosterone measurements on LIB and RES diets. Similar relationships were seen with urine aldosterone measurements and the integrated SAUSSI (Table 3).

In addition to providing an additive integration of associations of aldosterone measures on either diet alone, the SASSI and SAUSSI also seemed to distinguish individuals with MetS. Although the MetS definition does not include age, sex, and race (potential cardiometabolic risk factors that associate with aldosterone measurements in Tables 2 and 3), subjects with MetS had a higher SASSI and a nonsignificant trend toward higher SAUSSI values when compared with those without MetS (SASSI: 0.41±0.36 versus 0.33±0.32, P=0.01; SAUSSI: 0.42±0.59 versus 0.34±0.48, P=0.15), indicating an association between MetS and higher aldosterone suppression-to-stimulation ratios. We evaluated the impact of how successive components of the MetS would affect physiological aldosterone responses. In comparison with healthy subjects who lack any component of the MetS (zero components), those with increasing numbers of components exhibited a failure to suppress serum and urinary aldosterone on LIB diet and a failure to appropriately stimulate aldosterone on RES diet (Figure 2A, 2B, 2D, and 2E). In reflection of this dampening of the physiological range of aldosterone with progressive MetS components, both the SASSI and SAUSSI were observed to be higher, and strongly associated, with a greater number of MetS components (Figure 2C and 2F).

**Predicting Aggregate Cardiometabolic Risk Using SASSI and SAUSSI**

We examined the sensitivity and specificity for identifying healthy individuals (zero MetS components) using SASSI or SAUSSI, when compared with individuals with any 1 single MetS component. Both the SASSI and SAUSSI displayed a higher sensitivity for distinguishing individuals with zero cardiometabolic risk factors when compared with single serum or urinary measures of aldosterone on either diet (86% for SASSI, 83% for SAUSSI) (Table S2). In contrast, the ability to distinguish healthy individuals from any of the remaining subjects with 1, 2, 3, or 4 MetS components was not remarkably different among aldosterone measures (Table S2).

### Table 2. Univariate Relationships Between Serum Aldosterone Measurements and Individual Cardiometabolic Parameters

<table>
<thead>
<tr>
<th>Cardiometabolic Parameters</th>
<th>LIB Diet Serum Aldosterone</th>
<th>RES Diet Serum Aldosterone</th>
<th>SASSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P Value</td>
<td>β</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.3</td>
<td>−0.43</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>−0.35</td>
<td>0.2</td>
<td>−4.34</td>
</tr>
<tr>
<td>Race (black)</td>
<td>−0.56</td>
<td>0.7</td>
<td>−1.71</td>
</tr>
<tr>
<td>SBP</td>
<td>0.04</td>
<td>&lt;0.0001</td>
<td>−0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>0.07</td>
<td>0.05</td>
<td>−0.36</td>
</tr>
<tr>
<td>HDL</td>
<td>−0.02</td>
<td>0.003</td>
<td>−0.07</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.004</td>
<td>0.02</td>
<td>−0.002</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.14</td>
<td>0.06</td>
<td>−0.06</td>
</tr>
</tbody>
</table>

Effect estimates (β) and probability values are presented for each variable. BMI indicates body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; LIB, liberal; RES, restricted; SASSI, sodium-modulated aldosterone suppression-stimulation index for serum; SAUSSI, sodium-modulated aldosterone suppression-stimulation index for urine; and SBP, systolic blood pressure.

### Table 3. Univariate Relationships Between Urinary Aldosterone Measurements and Individual Cardiometabolic Parameters

<table>
<thead>
<tr>
<th>Cardiometabolic Parameters</th>
<th>LIB Diet Urine Aldosterone</th>
<th>RES Diet Urine Aldosterone</th>
<th>SAUSSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P Value</td>
<td>β</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>0.2</td>
<td>−1.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>−0.05</td>
<td>0.9</td>
<td>1.99</td>
</tr>
<tr>
<td>Race (black)</td>
<td>−1.26</td>
<td>0.04</td>
<td>−10.11</td>
</tr>
<tr>
<td>SBP</td>
<td>0.05</td>
<td>&lt;0.0001</td>
<td>−0.35</td>
</tr>
<tr>
<td>BMI</td>
<td>0.11</td>
<td>0.1</td>
<td>−1.03</td>
</tr>
<tr>
<td>HDL</td>
<td>−0.03</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.007</td>
<td>0.03</td>
<td>−0.07</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>−0.0004</td>
<td>0.9</td>
<td>−0.67</td>
</tr>
</tbody>
</table>

Effect estimates (β) and probability values are presented for each variable. BMI indicates body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; LIB, liberal; RES, restricted; SASSI, sodium-modulated aldosterone suppression-stimulation index for serum; SAUSSI, sodium-modulated aldosterone suppression-stimulation index for urine; and SBP, systolic blood pressure.
Is Abnormal Aldosterone Physiology a Consequence of a Primary Adrenal Defect or Secondary to Other Known Regulators of Aldosterone?

We explored whether the observed relationships between aldosterone responses and components of the MetS were attributable to a primary dysfunction of the adrenal glands or driven by other factors known to influence adrenal aldosterone physiology, such as AngII activity, serum potassium, or corticotropin (ACTH).

AngII Activity

We used measures of PRA as a surrogate for AngII because it is known to be highly correlated with AngII concentrations. In logistic regression models adjusted for age, sex, and race, an inability to suppress aldosterone or PRA on LIB diet predicted the odds of having MetS (Figure 3, top row). Progressive impairments in physiological aldosterone responses to dietary sodium manipulations (higher SASSI) were associated with higher odds of having MetS, but impaired PRA responses to dietary sodium manipulation (PRA on LIB:PRA on RES) were not (Figure 3, middle row). Like the SASSI, higher SASSI-II values were also associated with the odds of having MetS, suggesting that a blunted range of adrenal aldosterone responsiveness (and not endogenous PRA or AngII) was correlated with MetS (Figure 3, bottom row).

Serum Potassium

Serum potassium, a major regulator of aldosterone, was no different in those with MetS versus without MetS (LIB diet: 4.16±0.32 versus 4.16±0.34 mmol/L, P=0.90; RES diet: 4.18±0.33 versus 4.25±0.36 mmol/L, P=0.08). There was no association between increasing components of the MetS and

Figure 2. The association between the number of successive components of the metabolic syndrome (MetS) and aldosterone measures. Serum aldosterone concentrations on liberal (LIB) diet (A) and restricted (RES) diet (B) are paralleled with urinary aldosterone excretion rates on LIB diet (D) and RES diet (E). Serum measures are expressed as the SASSI with respect to MetS components (C) and urine measures are expressed as the SAUSSI (F). Data are presented as box plots, where boxes represent the 25th to 75th percentiles and black horizontal dashes represent the median value. SASSI indicates sodium-modulated aldosterone suppression-stimulation index for serum; and SAUSSI, sodium-modulated aldosterone suppression-stimulation index for urine.
serum potassium on either dietary condition \((P=0.50\) for LIB diet and \(P=0.10\) for RES diet).

**ACTH**

We used serum cortisol measures as a surrogate for ACTH, which was not directly measured. Serum cortisol levels did not differ between individuals with MetS versus without MetS on either diet (LIB diet: \(10.8\pm4.0\) versus \(11.3\pm4.5\) pg/mL, \(P=0.30\); RES diet: \(11.5\pm3.8\) versus \(12.1\pm4.5\) pg/mL, \(P=0.20\)) and were not associated with increasing components of the MetS on either LIB (\(P=0.30\)) or RES (\(P=0.20\)) diets.

**Discussion**

Our findings show strong associations between abnormal aldosterone physiology and individual cardiometabolic risk factors and suggest that progressive clustering of risk factors, as seen in the MetS, is also associated with pathophysiologic aldosterone regulation. These findings build on, and integrate, previous reports which suggest that an inability to appropriately stimulate\(^{14,17,18,33}\) or suppress\(^{7,8,19}\) aldosterone in response to physiological stimuli is associated with cardiometabolic disease. Our study is distinguished from previous studies that evaluated the role of aldosterone in disease in that it analyzed a very large sample size of subjects and used novel indices to represent dynamic aldosterone physiology. Although static aldosterone measurements in a specific environmental milieu (LIB diet or RES diet) may predict some cardiometabolic risk, our findings show that an index of aldosterone physiology that reflects the entire dynamic of sodium-induced aldosterone regulation provides a more complete integration of cardiometabolic risk associations (Tables 2 and 3). Our novel indices of aldosterone regulation not only associated with individual cardiometabolic risk variables but also were sensitive at distinguishing healthy individuals from those with mild cardiometabolic risk, and predicted the odds of having MetS and the severity of MetS. Furthermore, our analyses suggest that the abnormal aldosterone physiology seen with the progressive accrual of cardiometabolic risk factors is independent of demographic variables and known aldosterone secretagogues. In totality, these findings provide new insights into the role of aldosterone regulation in disease: cardiometabolic derangements may be caused by, or result in, progressive dysregulation of physiological aldosterone suppression and stimulation.

Our findings extend and clarify those of others before us. Previous cross-sectional studies, which often lacked control of environmental confounders of aldosterone, found that higher aldosterone levels were associated with an increased prevalence of MetS.\(^{6,9,10}\) Conversely, a large case–control study of \(\approx1800\) individuals found no difference in glucose and lipid values between individuals with and without primary hyperaldosteronism.\(^{34}\) With our strict study design, we confirm that higher aldosterone levels on a fixed diet of LIB sodium intake associate with multiple cardiometabolic risk factors. We extend these findings to show that the inability to appropriately stimulate aldosterone with sodium restriction also associates with similar risk factors, but in addition correlates with other risk factors (such as older age), which are not associated with the lack of aldosterone suppression on LIB sodium intake. These associations support our initial hypothesis that an integrated assessment of the dynamic range of aldosterone (suppression and stimulation) may better characterize the pathophysiologic role aldosterone plays in cardiometabolic diseases. Indeed, our integrated indices of aldosterone physiology associated with all of the cardiometabolic variables that correlated with aldosterone levels on either LIB diet or RES diet. Although it is not clear why some risk factors associate with abnormal aldosterone suppression, whereas others associate with abnormal aldosterone stimulation, our findings indicate that knowledge of the full range of adrenal aldosterone regulation may be important in understanding the pathogenesis of aldosterone-associated cardiometabolic diseases.

We used the MetS as an example of a heterogeneous clustering of cardiometabolic risk factors. Although MetS does not include important aldosterone-associated variables, such as age and race, our findings still suggest that the presence of any single MetS component is associated with a significant alteration in aldosterone physiology such that it is distinguished from that of a healthy individual. In contrast, with the successive accrual of MetS components, the dampening of the physiological aldosterone range seems to plateau (Figure 2C and 2F). On the basis of these observations, we speculate that the association between cardiometabolic risk factors and aldosterone physiology is most notable in the early development of cardiometabolic disease. With the progressive accrual of cardiometabolic risk factors, the dynamic range of aldosterone may approach a fixed asymptote that diminishes its ability to distinguish additional risk. Measurements of the SASSI or SAUSSI are not simple, not generalizable, and are unlikely to be adopted on a large scale. Our study does not support the use of these indices as diagnostics for disease or risk; however, it does provide novel insights in the dynamic and subtle alterations in adrenal physiology that occur with cardiometabolic inhibition.
We thank the fellows, trainees, and nursing staff who have contributed to the studies involving the HyperPath cohort.

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Disclosures

None.

References

Novelty and Significance

What Is New?

- We developed and tested novel indices (sodium-modulated aldosterone suppression-stimulation index for serum and for urine) to reflect the dynamic physiological range of aldosterone in response to dietary sodium modulation.

What Is Relevant?

- Integrated indices of aldosterone suppression-to-stimulation associate strongly with individual cardiometabolic risk factors, predict the odds and severity of metabolic syndrome, and discriminate healthy individuals from those with even mild cardiometabolic risk.

Summary

Abnormal aldosterone physiology, when represented by integrated indices that reflect the extremes of dietary sodium modulations, strongly predicts cardiometabolic risk factors and provides novel insights into the pathophysiology that may underlie aldosterone-mediated disease states.
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ABNORMAL ALDOSTERONE PHYSIOLOGY AND CARDIO-METABOLIC RISK FACTORS

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SHORT TITLE: Aldosterone Physiology and Cardio-Metabolic Risk

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TABLES: 2 FIGURES: 0; REFS: 6
SUPPLEMENTARY TABLES:

**Table S1: Conventional measures of aldosterone.** The table lists methods to assess aldosterone, the expected physiologic response, and its interpretation. Measures that were utilized in this study are indicated in the last column.

<table>
<thead>
<tr>
<th>Measure of Aldosterone</th>
<th>Abbreviation</th>
<th>Expected Physiologic Response</th>
<th>Interpretation</th>
<th>Measured in this Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random serum aldosterone</td>
<td>Serum aldosterone</td>
<td>variable</td>
<td>Prone to intra- and inter-individual variation induced by diet, posture, circadian rhythms, and stress.(^1,2)</td>
<td>No</td>
</tr>
<tr>
<td>Random 24 hour urine aldosterone</td>
<td>Urinary aldosterone</td>
<td>variable</td>
<td>Prone to intra- and inter-individual variation induced by diet, posture, and stress(^1)</td>
<td>No</td>
</tr>
<tr>
<td>Serum or urine aldosterone measures with subject in balance on a fixed liberal sodium diet</td>
<td>Serum aldosterone on LIB diet</td>
<td>↓↓↓</td>
<td>• Maximal suppression of aldosterone, with simultaneous suppression of ANGII and PRA(^1,3,4)</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum or urine aldosterone measures with subject in balance on a fixed restrictive sodium diet</td>
<td>Serum aldosterone on RES diet</td>
<td>↑↑</td>
<td>• Stimulated aldosterone, with simultaneous stimulation of ANGII and PRA(^1)</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum aldosterone following an infusion of angiotensin II on</td>
<td>ANGII stimulated serum aldosterone on RES diet</td>
<td>↑↑↑</td>
<td>• Stimulation of aldosterone, with a simultaneous suppression of endogenous PRA and ANGII, allows for</td>
<td>Yes</td>
</tr>
<tr>
<td>restrictive sodium diet</td>
<td>“uncoupling” of RAAS components(^6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Blunted stimulation may indicate abnormal adrenal responsiveness(^6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table S2: Sensitivity and Specificity of Aldosterone Measurements and Risk for Cardio-Metabolic Disease. The sensitivity and specificity for detecting zero versus any one component of the MetS, and the sensitivity and specificity for detecting zero versus any combination of MetS components.

<table>
<thead>
<tr>
<th>Zero versus any 1 MetS component</th>
<th>Aldosterone Measurements</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LIB Aldo Serum</td>
<td>0.79</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>RES Aldo Serum</td>
<td>0.65</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>SASSI</td>
<td>0.86</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>LIB Aldo Urine</td>
<td>0.78</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>RES Aldo Urine</td>
<td>0.62</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>SAUSSI</td>
<td>0.83</td>
<td>0.29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zero versus All (1, 2, 3, or 4 MetS components)</th>
<th>Aldosterone Measurements</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LIB Aldo Serum</td>
<td>0.94</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>RES Aldo Serum</td>
<td>0.62</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>SASSI</td>
<td>0.91</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>LIB Aldo Urine</td>
<td>0.86</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>RES Aldo Urine</td>
<td>0.43</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>SAUSSI</td>
<td>0.95</td>
<td>0.28</td>
</tr>
</tbody>
</table>
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