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ABNORMAL ALDOSTERONE PHYSIOLOGY AND CARDIO-METABOLIC RISK FACTORS

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Abstract

Abnormal aldosterone physiology has been implicated in the pathogenesis of cardio-metabolic 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 cardio-metabolic 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 cardio-metabolic risk factors. We performed cross-sectional analyses on 539 subjects studied on liberal (LIB) and restricted (RES) sodium diets with serum and urinary aldosterone measurements. SASSI and SAUSSI were calculated as the ratio of aldosterone on LIB (maximally suppressed aldosterone) to aldosterone on RES (stimulated aldosterone) diets, and associated with risk factors using adjusted regression models. Cardio-metabolic risk factors associated with either impaired suppression of aldosterone on LIB diet, or impaired stimulation on RES diet, or both; in all of these individual cases, these risk factors associated with higher SASSI or SAUSSI. In the context of abnormalities that comprise the metabolic syndrome (MetS), there was a strong positive association between the number of MetS 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 MetS components (86% for SASSI and 83% for SAUSSI). Assessing the physiologic range of aldosterone responses may provide greater insights into adrenal pathophysiology. Dysregulated aldosterone physiology may contribute to, and/or result from, early cardio-metabolic abnormalities.

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INTRODUCTION

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

Aldosterone dysregulation has been associated with cardio-metabolic 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 cardio-metabolic 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[7, 14, 19]. In contrast, induction of a very restricted sodium balance, or the infusion of exogenous angiotensin II (AngII), stimulate adrenal aldosterone secretion; a blunted stimulation of aldosterone in these settings has also been associated with similar cardio-metabolic 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 into the pathogenesis and treatment of cardio-metabolic derangements.

We developed a novel index to reflect physiologic aldosterone responses to dietary sodium manipulation. This index integrates aldosterone physiology via a ratio of aldosterone levels on a liberal sodium (LIB) diet to levels on a restricted (RES) sodium diet. In this manner, this integrated index captures physiologic 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 cardio-metabolic risk factors and with aggregate constellations of cardio-metabolic risk, such as the MetS. These findings could better define the development of abnormal aldosterone physiology with progressive cardio-metabolic 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 dataset consisting of individuals who underwent rigorous profiling of the RAAS under controlled conditions, was conducted. Five

centers contributed to this dataset: Brigham and Women's Hospital (Boston, MA, USA) , University of Utah Medical Center (Salt Lake City, UT,USA) , Hospital Broussais (Paris, France) , University of Rome (Rome Italy), and Vanderbilt University (Nashville, TN, USA). For this analysis, we included individuals who successfully completed all study procedures, and had complete data for all 4 components of the metabolic syndrome according to the World Health Organization (WHO) criteria[22] (hypertension, insulin resistance [fasting glucose and insulin], 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 gender are not a part of the MetS definition), we used the MetS as a model of a pre-defined, and well known, compounded cardio-metabolic risk state. The HyperPATH cohort characterized hypertension as a seated diastolic blood pressure of ≥ 100 mmHg off antihypertensive medications, ≥ 90 mmHg taking ≥ 1 medication, or treatment with ≥ 2 medications. Type 2 diabetes mellitus (T2DM) was defined per American Diabetes Association criteria [23]: fasting blood glucose ≥ 126 mg/dl, random blood glucose ≥ 140 mg/dl, HgA1c ≥ 6.5%, 2-hr OGTT blood glucose ≥ 200 mg/dl or a prior physician confirmed diabetes diagnosis [22]. A participant was considered to have the MetS if they had T2DM (see above criteria), impaired glucose tolerance (2-hr oral glucose tolerance test (OGTT) glucose >140 mg/dl [24], impaired fasting glucose (≥ 100 mg/dl ADA citation), or insulin resistance (upper tertile of HOMA-IR in the HyperPATH: HOMA-IR ≥ 3) plus two or more of the characteristics listed below:

1. Hypertension (see above definition)
2. Hyperlipidemia: triglycerides measurement greater than or equal to 150 mg/dl and/or high density lipoprotein (HDL) <35 mg/dl in men and <39 mg/dl in women.
3. Obesity: BMI ≥30 kg/m^2

Although other results from the HyperPATH cohort have been reported previously[14, 16–18], 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, EKG, and laboratory evaluation. Participants with known or suspected secondary hypertension, coronary artery disease, stroke, overt renal insufficiency (serum creatinine >1.5mg/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 prior coronary events at the screening exam 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 (IRB) of each site and informed consent was obtained prior to participant enrollment.

Study Protocol—Details of this protocol have been described previously[20]. In brief, to control for 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 prior to study, and beta blockers, calcium-channel blockers, and diuretics were discontinued for at least 2 weeks prior to the study. If necessary, participants were briefly given amlodipine for blood pressure (BP) control; however, this was discontinued 2 weeks prior to the start of the study procedures.

Participants completed two diets for 5–7 days each: liberal sodium (LIB) (200mmol/day) and restricted sodium (RES) (10mmol/day) with each diet also containing 100 mmol/day potassium and 20 mmol/day calcium. Upon completion of each diet phase, participants were admitted overnight to the Clinical Research Center (CRC). 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 (HDL), low density lipoprotein (LDL), triglycerides, plasma renin activity (PRA), serum aldosterone, and blood pressure were obtained in the morning after overnight supine rest using standardized and validated methods as previously described [16, 25]. After baseline blood draws were collected on RES diet, an infusion of angiotensin II (ANGII) (Bachem AG, Bubendorf, Switzerland) (3ng/kg/min for 60 min) was administered as previously described [25], and measurements for serum aldosterone and PRA were repeated at the end of the infusion. Insulin resistance was measured using the homeostatic model assessment (HOMA-IR) as previously described [26].

On the morning of the 5th day of the LIB diet, a portion of the non-diabetic participants reported to the ambulatory clinical research center and received a 75 g oral glucose tolerance test (OGTT). The OGTT 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 cardio-metabolic risk factors. Among the many methods to measure the RAAS (Table S1), 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 to dietary sodium-stimulated aldosterone) (Table 1). The ratio of 24h urinary aldosterone excretion on both LIB and RES diets was used to calculate the SAUSSI (ratio of dietary sodium suppressed to dietary sodium stimulated urinary aldosterone excretion). The ratio of the supine serum aldosterone on LIB diet to the serum aldosterone following 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 (Table 1). The SASSI-II was developed to provide more information than the SASSI or SAUSSI might alone, since ANGII stimulation on RES diet provides a measure of adrenal aldosterone stimulation that is independent of other endogenous RAAS components (ANGII and PRA). Thus, while the physiologic responses of PRA, ANGII, and aldosterone are expected to be parallel and correlated in a dietary sodium-modulated index such as the SASSI, the SASSI-II is expected to distinguish the contributions of aldosterone versus other RAAS components.

Although plasma ANGII measurements were not available on the vast majority of participants, single supine PRA measurements were available on LIB and RES diets for all subjects. The ratio of these measurements (PRA on LIB diet:PRA on RES diet) was used to evaluate the physiologic range of PRA to dietary sodium manipulation. In addition, PRA was measured after the infusion of ANGII on RES diet, and used in an index to parallel the SASSI-II (PRA on LIB: PRA on RES after ANGII).

Statistical Analyses

Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, N.C., U.S.A.). Population characteristics for individuals with and without MetS were compared using a Student's t-test. A chi-square analysis was used for comparison of categorical variables. Data are represented as means ± standard deviation. The main analyses for this study included: 1) univariate regression analyses to analyze the relationship between individual cardio-metablic risk factors and measures of aldosterone; 2) 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, gender, and

race[29–31]. Sensitivity and specificity analyses were conducted to evaluate whether physiologic aldosterone measurements could distinguish healthy individuals (zero MetS components) from those with any one MetS component (0 versus 1) or those with any combination of MetS components (0 versus 1, 2, 3, or 4). Since specific aldosterone measurements associated with cardio-metabolic risk have not been established, we chose cut-points for the sensitivity and specificity analyses based on the highest tertile value for each aldosterone measurement[32]. All statistical tests were 2-sided. Significance is indicated for $p<0.05$.

RESULTS

The Study Population

Twenty-six percent of the study population had MetS, and as expected, these individuals were older in age, and had higher BMI, fasting blood glucose, and blood pressure (BP) (Table 2). Consistent with prior reports[6, 9, 10], aldosterone concentrations and PRA on LIB diet were significantly higher in individuals with MetS compared to those without MetS. In contrast, a non-significant trend towards lower serum and urinary aldosterone levels was observed during RES diet conditions.

The SASSI and SAUSSI as Predictors of Individual and Aggregate Cardio-Metabolic Risk

We evaluated the correlation between aldosterone measurements and individual cardio-metabolic 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 3a). 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 gender, 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 3b).

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, gender, and race (potential cardio-metabolic risk factors that associate with aldosterone measurements in Table 3a and 3b), subjects with MetS had a higher SASSI and a non-significant trend towards higher SAUSSI values when compared to those without MetS (SASSI: 0.41 ± 0.36 vs. 0.33 ± 0.32, $P=0.01$; SAUSSI: 0.42 ± 0.59 vs. 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 physiologic aldosterone responses. In comparison to 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 1 A–B, 1D–E). In reflection of this dampening of the physiologic 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 1C and 1F).

Predicting Aggregate Cardio-Metabolic Risk Using SASSI and SAUSSI

We examined the sensitivity and specificity for identifying healthy individuals (zero MetS components) using SASSI or SAUSSI, when compared to individuals with any one single MetS component. Both the SASSI and SAUSSI displayed a higher sensitivity for

distinguishing individuals with zero cardio-metabolic risk factors when compared to 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).

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 due 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 since it is known to be highly correlated with ANGII concentrations. In logistic regression models adjusted for age, gender, and race, an inability to suppress aldosterone or PRA on LIB diet predicted the odds of having MetS (Table 4 – top row). Progressive impairments in physiologic aldosterone responses to dietary sodium manipulations (higher SASSI) were associated with a higher odds of having MetS, but impaired PRA responses to dietary sodium manipulation (PRA on LIB:PRA on RES) were not (Table 4 – 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 (Table 4 – bottom row).

Serum Potassium

Serum potassium, a major regulator of aldosterone, was no different in those with versus without MetS (LIB diet: 4.16 ± 0.32 vs 4.16 ± 0.34 mmol/L p=0.90; RES diet: 4.18 ± 0.33 vs 4.25 ± 0.36 mmol/L, p=0.08). There was no association between increasing components of the MetS and 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 versus without the MetS on either diet (LIB diet: 10.8 ± 4.0 vs 11.3 ± 4.5 pg/mL, p=0.30; RES diet: 11.5 ± 3.8 vs 12.1 ± 4.5 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 with individual cardio-metabolic risk factors, and suggest that progressive clustering of risk factors, as seen in the MetS, are also associated with pathophysiologic aldosterone regulation. These findings build upon, and integrate, prior reports which suggest that an inability to appropriately stimulate[14, 17, 18, 33] or suppress[7, 8, 19] aldosterone in response to physiologic stimuli is associated with cardio-metabolic 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 employed novel indices to represent dynamic aldosterone physiology. Whereas static aldosterone measurements in a specific environmental milieu (LIB diet or RES diet) may predict some cardio-metabolic 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 cardio-metabolic risk associations (Table 3). Our novel indices of aldosterone regulation not only associated with individual cardio-metabolic risk variables, but were also sensitive at distinguishing healthy individuals from those with mild cardio-metabolic 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 cardio-metabolic 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: cardio-metabolic derangements may be caused by, or result in, progressive dysregulation of physiologic aldosterone suppression and/or stimulation.

Our findings extend and clarify those of others before us. Prior cross-sectional studies, that often lacked control of environmental confounders of aldosterone, found that higher aldosterone levels were associated with an increased prevalence of MetS[9 10 6]. Conversely, a large case-control study of approximately 1,800 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 liberal sodium intake associate with multiple cardio-metabolic 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 liberal 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 cardio-metabolic diseases. Indeed, our integrated indices of aldosterone physiology associated with all of the cardio-metabolic variables that correlated with aldosterone levels on either LIB diet and/or RES diet. Although it is not clear why some risk factors associate with abnormal aldosterone suppression while 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 cardio-metabolic diseases.

We used the MetS as an example of a heterogeneous clustering of cardio-metabolic 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 physiologic aldosterone range appears to plateau (Figures 1C and 1F). Based on these observations, we speculate that the association between cardio-metabolic risk factors and aldosterone physiology is most notable in the *early* development of cardio-metabolic disease. With the progressive accrual of cardio-metabolic 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 into the dynamic and subtle alterations in adrenal physiology that occur with cardio-metabolic disease. This knowledge may help guide future therapies and prevention measures to lower cardio-metabolic risk.

What mechanisms may account for the dampening of the physiologic aldosterone range we observed with progressive cardio-metabolic risk factors? One could postulate that the progressive accumulation of MetS components results in abnormalities in adrenal aldosterone regulation, or that alternatively, a predisposition to abnormal adrenal physiology

increases the likelihood of developing MetS components. We explored potential mechanisms by evaluating known regulators of aldosterone, such as PRA-ANGII axis, ACTH, and serum potassium; however, observed no meaningful correlations to suggest that these factors were responsible for the resultant aldosterone responses. Therefore, we speculate that the development of abnormal aldosterone physiology with cardio-metabolic disease is due to either a primary adrenal gland dysfunction, or due to other unknown or unmeasured regulators of aldosterone (such as adipose tissue) that warrant further characterization[35–37].

Our study has several strengths. Our sample size was large (>500 subjects) and included more than 1,000 inpatient study visits (2 per subject) dedicated to characterizing the RAAS under tightly controlled environmental conditions. Hormonal measurements were conducted after participants ingested a diet that controlled electrolytes known to affect RAAS components in humans[38, 39], and dietary compliance was confirmed with urinary assessments. Subjects were withdrawn from all interfering medications to increase the confidence in RAAS measures. Further, participants were admitted to an in-patient Clinical Research Center and studied after overnight supine rest. Aldosterone was characterized using serum and urinary measures, and we observed parallel findings with both assessments, highlighting the robust nature of these relationships. Notable limitations of our study include its cross-sectional nature. We cannot confirm a causal relationship between inappropriate aldosterone physiology and cardio-metabolic risk factors or MetS. Our analyses were not designed to evaluate the diagnostic utility of our indices, which are impractical; rather the focus was to provide insights into adrenal pathophysiology that may underlie cardio-metabolic disease states. Interventional studies to evaluate the effect of RAAS antagonists in individuals with abnormal SASSI/SAUSSI are needed to better assess causality.

PERSPECTIVES

In summary, we conclude that abnormal aldosterone physiology, when represented by integrated indices that reflect the extremes of dietary sodium modulations, strongly predicts individual and compounded cardio-metabolic risk factors. The earliest manifestations of cardio-metabolic derangements may exhibit abnormalities in aldosterone suppression and/or stimulation that are detected by integrated indices such as the SASSI and SAUSSI. Future studies to investigate the mechanisms underlying the blunting of the dynamic range of aldosterone may identify new therapeutic approaches to prevent or treat cardio-metabolic risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NOVELTY and SIGNIFICANCE

1) What is New? We developed and tested novel indices (SASSI and SAUSSI) to reflect the dynamic physiologic range of aldosterone in response to dietary sodium modulation.

2) What is Relevant? Integrated indices of aldosterone suppression-to-stimulation associate strongly with individual cardio-metabolic risk factors, predict the odds and severity of metabolic syndrome, and discriminate healthy individuals from those with even mild cardio-metabolic risk.

Summary: Abnormal aldosterone physiology, when represented by integrated indices that reflect the extremes of dietary sodium modulations, strongly predicts cardio-metabolic risk factors, and provides novel insights into the pathophysiology that may underlie aldosterone-mediated disease states.

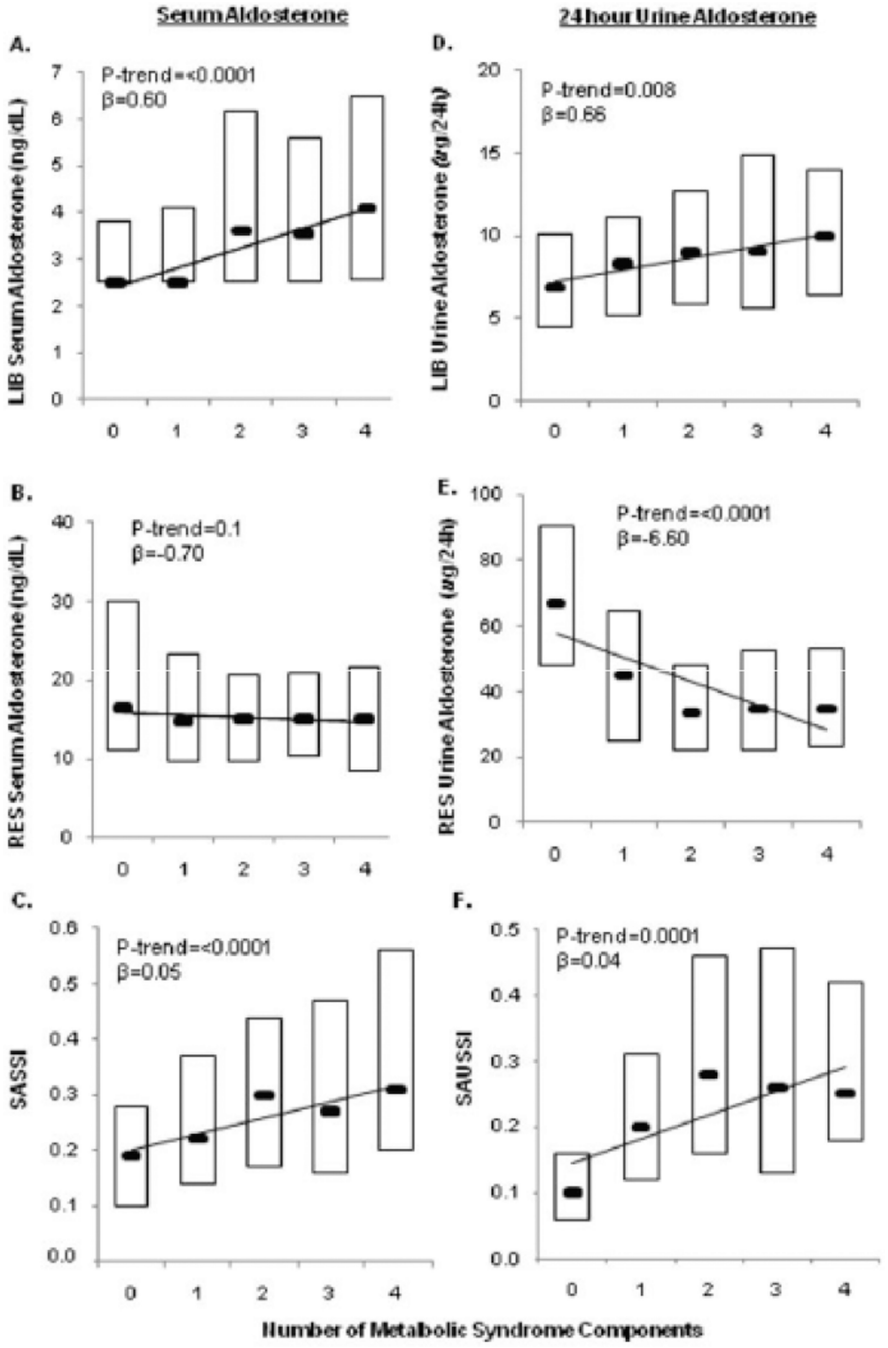

Figure 1. The association of between the number of successive components of the MetS and aldosterone measures

Serum aldosterone concentrations are on LIB diet (A) and 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 25^{th}-75^{th} percentiles and black horizontal dashes represent the median value.

Table 1
New Indices to Represent Aldosterone Physiology

The table lists novel indices that were devised in this study to represent physiologic aldosterone responses and their interpretation.

Index of Aldosterone Physiology	Abbreviation	Interpretation
Serum aldosterone on LIB diet --- Serum aldosterone on RES diet	SASSI	• Integrates the benefits of both dietary sodium-suppressive and dietary sodium-stimulatory responses, and minimizes the limitations of each • A high SASSI indicates a dampening of the physiologic range of aldosterone secretion to dietary sodium manipulation
Serum aldosterone on LIB diet --- ANGII stimulated serum aldosterone on RES diet	SASSI-II	• An alternative version of the SASSI that employs ANGII to stimulate aldosterone on RES diet. • Permits isolated evaluation of aldosterone physiology, since other endogenous RAAS components are suppressed by ANGII infusion.
Urinary aldosterone on LIB diet --- Urinary aldosterone on RES diet	SAUSSI	• A urinary surrogate of SASSI • Urinary responses can be used to confirm serum aldosterone observations.

Table 2

Baseline characteristics of the study population based on MetS status

Where applicable, variables are depicted when subjects were maintained on LIB and RES diets. Values are represented as means±standard deviation.

Characteristics	MetS (−)	MetS(+)	p value
N	398	141	
Age (years)	45.9±10.7	48.8±8.7	0.004
Female Gender (%)	199 (50%)	48 (34%)	0.001
Race			
Caucasian (%)	336(84%)	109(78%)	0.08
African American (%)	44(11%)	26 (18%)	0.08
Other (%)	18 (5%)	6 (4%)	
Body Mass Index (kg/m^2)			
LIB diet	26.5±3.7	30.7±4.0	<0.0001
RES diet	25.8±3.7	29.9±4.1	<0.0001
Fasting Blood Glucose (mg/dl)			
LIB diet	88.8±16.8	103.9±21.3	<0.0001
RES diet	96.0±32.6	104.9±22.6	<0.0001
Mean Arterial Pressure (mmHg)			
LIB diet	97.2±16.0	106.7±13.7	<0.0001
RES diet	88.8±13.2	97.6±11.7	<0.0001
Serum Aldosterone Baseline (ng/dl)			
LIB diet	4.3±2.9	5.3±3.9	0.0007
RES diet	18.0±12.3	17.5±11.0	0.7
Urinary Aldosterone Excretion Rate (mcg/24h)			
LIB diet	10.1±7.9	13.8±29.4	<0.0001
RES diet	45.9±29.8	41.9±26.9	0.2
Plasma Renin Activity (ng/mL/h)			
LIB diet	0.43±0.43	0.63±1.2	<0.01
RES diet	2.47±2.0	2.79±3.0	0.20
Urinary Sodium (mmol/24hrs)			
Lib diet	240.8±66.2	250.1±74.5	0.20
RES diet	12.7±8.9	13.8±8.3	0.20
Urinary Potassium (mEq/24hrs)			
Lib diet	72.5±24.3	76.6±24.1	0.1
RES diet	73.3±19.6	71.8±20.0	0.4

Table 3

Univariate Relationships Between Serum (A) and Urinary (B) Aldosterone Measurements and Individual Cardio-Metabolic Parameters

Effect estimates (β) and P-values are presented for each variable.

A)

Cardio-Metabolic Parameters	LIB Diet Serum Aldosterone		RES Diet Serum Aldosterone		SASSI	
	β	p value	β	p value	β	p value
Age	0.01	0.3	−0.43	<0.0001*	0.007	<0.0001*
Gender (male)	−0.35	0.2	−4.34	0.6	0.03	<0.0001*
Race (African American)	−0.56	0.7	−1.71	0.6	−0.02	0.8
SBP	0.04	<0.0001*	−0.02	0.4	0.004	<0.0001*
BMI	0.07	0.05*	−0.36	0.004*	0.01	0.001*
HDL	−0.02	0.003*	−0.07	0.06	0.00004	0.9
Triglycerides	0.004	0.02*	−0.002	0.7	0.0003	0.08
HOMA-IR	0.14	0.06	−0.06	0.8	0.01	0.2

B)

Cardio-Metabolic Parameters	LIB Diet Urine Aldosterone		RES Diet Urine Aldosterone		SAUSSI	
	β	p value	β	p value	β	p value
Age	0.04	0.2	−1.001	<0.0001*	0.007	<0.0001*
Gender (male)	−0.05	0.9	1.99	0.4	0.01	0.7
Race (African American)	−1.26	0.04*	−10.11	0.03*	0.18	0.7
SBP	0.05	<0.0001*	−0.35	<0.0001*	0.004	<0.0001*
BMI	0.11	0.1	−1.03	0.0008*	0.003	0.4
HDL	−0.03	0.08	0.18	0.05*	−0.001	0.2
Triglycerides	0.007	0.03*	−0.07	<0.0001*	0.0002	0.09
HOMA-IR	−0.0004	0.9	−0.67	0.2	−0.01	0.05*

Table 4
Physiologic RAAS Measurements and the Odds for Metabolic Syndrome

Every aldosterone measurement, regardless of interventional provocation, significantly predicted the odds of having MetS (yes/no). In contrast, this was not true of all PRA measurements. Values represent odds ratios and 95% confidence intervals.

Physiologic Aldosterone Measurements		Aldosterone Measure	PRA Measure	Physiologic PRA Measurements
Serum aldosterone on LIB diet		1.10 [1.04–1.16] **	2.10 [1.40–3.20]***	**Supine PRA on LIB diet**
LIB diet aldosterone ---------- **RES diet aldosterone**	**(SASSI)**	2.20 [1.2–3.9] **	1.50 [0.94–2.40]	**PRA on LIB diet** ---------- **PRA on RES diet**
LIB diet aldosterone ---------- **RES diet ANGII-stimulated aldosterone**	**(SASSI-II)**	8.33 [1.16–60.1] *	1.40 [0.87–2.20]	**PRA on LIB diet** ---------- **PRA after ANGII stimulation on RES diet**

* P<0.05,

** P<0.01,

****P<0.001.