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Research paper

The stress, salt excretion, and nighttime blood pressure (SABRE) study: Rationale and study design

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ABSTRACT

Background: Abnormal diurnal patterns of blood pressure (BP) on ambulatory BP monitoring (ABPM), defined by reduced BP dipping or elevated nighttime BP, are associated with increased risk for adverse cardiovascular events. Psychological stress is associated with abnormal diurnal patterns of BP. Exposure to an acute stressor (e.g., mental stress task) normally increases urinary sodium excretion. However, some individuals have sodium retention after stress provocation, revealing substantial between-person variability in the degree of stress-induced sodium excretion. Prior research suggests urinary sodium excretion that does not occur during the daytime may shift toward the nighttime, accompanied by an increase in nighttime BP. Associations between psychological stress and the diurnal patterns of sodium excretion and BP are not yet fully understood.

Design: The study is conducted in both the laboratory and naturalistic environment with a multi-racial/ethnic sample of 211 healthy adults. In the laboratory, change in urinary sodium excretion in response to mental stress tasks is examined with pre-/post-stress assessments of sodium excretion. Changes in angiotensin-II, catecholamines, BP, heart rate, endothelin-1, and cortisol are also assessed. In the 24-hour naturalistic environment, the diurnal patterns of sodium excretion and systolic BP are assessed as daytime-to-nighttime ratio of sodium excretion and ABPM, respectively. Ecological momentary assessments of perceived stress are also collected.

Summary: The SABRE study investigates previously unexplored associations between stress-induced urinary excretion in the laboratory, diurnal patterns of sodium excretion and BP in the naturalistic environment, and ecological stress. It has high potential to advance our understanding of the role of psychological stress in hypertension.

1. Background

Among the many risk factors that contribute to incident cardiovascular diseases (CVD) including coronary artery disease, heart failure, and stroke, elevated blood pressure (BP) or hypertension, is the most prevalent [1,2]. In individuals with regular sleep-wake patterns, BP has a diurnal rhythm, with the highest BP occurring during the daytime while awake and the lowest BP occurring during nighttime while asleep [3–5]. Normally, the percent reduction of BP from daytime to nighttime is 10–20%, but some individuals have non-dipping BP defined as a reduction of BP <10% [3]. The population prevalence of non-dipping BP ranges from 18% to 64%, and some studies have shown that non-dipping BP dipping is associated with increased CVD risk [5–11]. BP dipping status is typically assessed using ambulatory BP monitoring (ABPM), which measures BP automatically at preset intervals over a 24-hour period [3–5].

One possible mechanism underlying non-dipping BP is the disruption of the diurnal pattern of urinary sodium excretion. Similar to BP, urinary

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sodium excretion usually peaks during the daytime and dips during the nighttime. The normal response to dietary sodium intake during the daytime is increased BP, which leads to increased urinary sodium excretion [12–14]. It has been hypothesized that when urinary sodium excretion does not occur normally during the daytime, it shifts toward the nighttime period [15]. This shift may be accompanied by an increase in nighttime BP, which may result in non-dipping, to facilitate continued sodium excretion via increased renal perfusion pressure [15,16]. Studies have demonstrated an association between an abnormal diurnal pattern of sodium excretion and an abnormal diurnal pattern of BP. However, these studies did not control for dietary sodium intake [17,18], and it remains unclear whether this relationship is independent of sodium intake or sodium sensitivity.

Exposure to an acute psychological stressor in the laboratory such as a mental stress task increases urinary sodium excretion [19–29]. However, there is substantial between-person variability in stress-induced sodium excretion; some individuals have reduced sodium excretion after stress provocation, despite an increase in BP [19,27,30]. It is plausible that individuals with lower stress-induced sodium excretion who experience psychological stress during the day may have a shift of urinary sodium excretion toward the night due to an impaired ability to excrete sodium during the day [15,16,31]. This shift toward nighttime sodium excretion may be associated with a smaller decline in BP from the daytime to the nighttime periods, resulting in reduced BP dipping and elevated nighttime BP. Therefore, lower stress-induced sodium excretion in the laboratory may be associated with an abnormal diurnal pattern of BP.

Among individuals who have lower stress-induced sodium excretion in the laboratory, higher levels of ecological stress (i.e. more frequent stressful events) during the day, may further exacerbate the stress-induced shift toward nighttime sodium excretion. Therefore, ecological levels of stress may modify the association between stress-induced sodium excretion and the diurnal pattern of sodium excretion.

Several factors are associated with reduced stress-induced sodium excretion including male sex, African American race, greater body mass index (BMI), parental history of hypertension, and higher office BP [19,22,23,26,28,29]. Further, activation of the renin-angiotensin-aldosterone system and autonomic system, and reduction in urinary excretion of endothelin-1 from psychological stress may underlie lower stress-induced sodium excretion [25,27,28,32,33].

2. Rationale and aims

For ensuring rigor and reproducibility and providing up-to-date information on the cross-cutting areas of cardiovascular prevention, hypertension, and behavioral medicine, herein, we describe our hypotheses as well as the planned study procedures for the Stress, sAlt excretion, and nighttime Blood pREssure (SABRE) study prior to its completion. The overall goal of the SABRE study is to examine whether urinary sodium excretion induced by psychological stress and its diurnal pattern is a biological mechanism that underlies an abnormal diurnal pattern of BP. Our theoretical model (Fig. 1) incorporates several concepts, including diurnal patterns of sodium excretion and BP, urinary sodium excretion in response to provoked stress, and the experience of ecological levels of stress, into a novel framework that may increase our understanding of the mechanisms underlying reduced BP dipping. This translational study utilizes laboratory measures along with collection of data in the naturalistic environment, including 24-hour ABPM and ecologic momentary assessments (EMA) of stress. Because high dietary sodium may result in high BP and an abnormal diurnal pattern of BP in individuals who are salt sensitive, all participants will receive a standardized diet with a fixed amount of sodium as well as potassium prior to the laboratory and ambulatory measures. Finally, this study will focus on mechanisms of reduced BP dipping unrelated to sleep apnea, chronic insomnia, and kidney disease, factors that are also associated with reduced BP dipping.

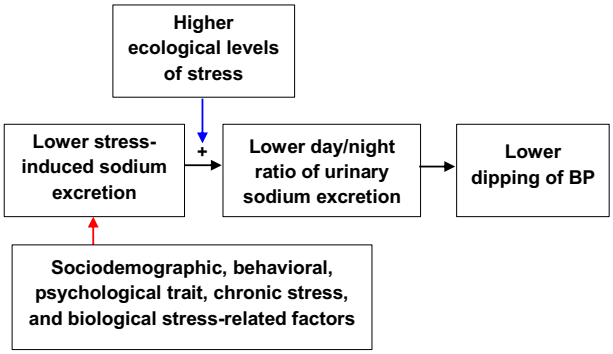

Fig. 1. Theoretical Model of Blood Pressure, Sodium Excretion, and Ecological Stress
Black arrows represent primary aims, the blue arrow represents the secondary aim, and the red arrow represents the exploratory aim. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The goal of the SABRE study is to address the following specific aims:

Primary Aim 1. To examine the association between urinary sodium excretion after provoked psychological stress and the diurnal pattern of sodium excretion. We hypothesize that reduced sodium excretion after laboratory stress induction will be associated with a lower daytime-to-nighttime ratio of urinary sodium excretion in the naturalistic environment.

Primary Aim 2. To examine the association between the diurnal pattern of sodium excretion and the diurnal pattern of BP. We hypothesize that a lower ratio of daytime-to-nighttime urinary sodium excretion will be associated with lower BP dipping in the naturalistic environment.

Secondary Aim. To determine if the association between urinary sodium excretion after provoked stress and the diurnal pattern of sodium excretion is modified by ecological momentary levels of stress throughout the day.

Exploratory Aim. To determine the sociodemographic, behavioral, psychological trait, chronic stress, and biological stress-related factors that are associated with lower stress-induced sodium excretion.

3. Design

3.1. Study overview

The SABRE study will enroll 211 adult participants to undergo a three-day sodium- and potassium-controlled diet, a laboratory psychological stress induction, and an ecological monitoring period outside the laboratory environment. An overview of the study design is shown in Fig. 2.

3.2. Pilot study

In a SABRE pilot study (n = 30) conducted in 2015, we tested the feasibility of the study protocol and analyzed distributions of the study measures including stress-induced sodium excretion, daytime-to-nighttime ratio of urinary sodium excretion, and BP dipping, all of which were consistent with prior studies [8,17,18,23,28,34]. The current SABRE study utilizes a similar protocol, modified for the collection of additional measures.

3.3. Study population

Healthy adult participants ≥21 years are recruited through word of mouth and study flyers placed in the racially and ethnically diverse Washington Heights neighborhood, as well as through ClinicalTrials.gov

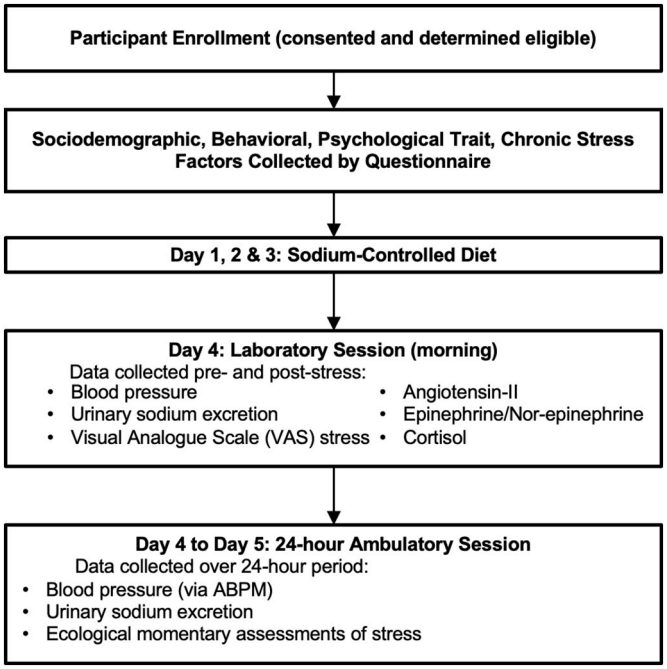

Fig. 2. Overview of study design.
VAS, visual analog scale.

and RecruitMe, a web-based registry for potential research participants at Columbia University Irving Medical Center (CUIMC). Participants complete a self-report initial screening survey administered through the online Qualtrics platform (Provo, UT) assessing inclusion and exclusion criteria (Table 1). Eligible individuals attend an enrollment visit to provide informed consent and to finalize study eligibility. Anthropometric values (height, weight, waist circumference) are also collected. Individuals meeting all eligibility criteria are provided with a link to an online questionnaire assessing sociodemographic, behavioral, psychological trait, and chronic stress factors (Table 2).

Our goal is to enroll 211 eligible participants for a final sample size of 200 participants with complete data: 11 (5%) are anticipated to withdraw from the study or have missing data for another reason. A final analytical sample size of 200 participants will provide adequate power to test our hypotheses, as described below. Target enrollment goals by sex, race, and ethnicity are shown in Table 3. As of September 1st, 2021, 179 have been enrolled.

Table 1
Eligibility criteria for the SABRE study.

Inclusion criteria
• Age 21 years or older • Screening BP <160/105 mmHg at enrollment, as determined by the mean of three separate measurements with one-minute interval rest periods
Exclusion criteria
• History of overt CVD (coronary heart disease, stroke, peripheral arterial disease, heart failure, permanent or recurring arrhythmias) • History of secondary hypertension • History of chronic kidney disease or other major medical condition(s) • History of diabetes or hyperlipidemia • Currently taking antihypertensive medications or other medications that are known to substantially affect BP (e.g., steroids, chronic anti-inflammatory medications) • Chronic insomnia, as determined by the Insomnia Symptom Questionnaire. • Moderate to severe sleep apnea, defined as an Apnea-Hypopnea Index ≥15, assessed using home polysomnography • Non-English speaking

Table 2
Sociodemographic, behavioral, psychological trait, and chronic stress measures collected in the study.

Sociodemographic	Demographics (age, sex, race and ethnicity, cultural background)
	Socioeconomic status: highest level of education attained, employment status, health insurance status, marital status, household income, household size
	12-Item Interpersonal Support Evaluation List Social Support Survey [44]
	Neighborhood and Social Environment Assessment [45]
Behavioral	Alcohol use [46]
	Smoking History (cigarettes and e-cigarettes) [47]
	Physical Activity using Paffenbarger scale [48]
Psychological trait	Modified Life Events and PTSD Checklist [49,50]
	50-Item Cook-Medley Hostility scale [51]
	Center for Epidemiological Studies Depression Scale [52]
	State-Trait Anxiety Inventory Y [53]
	Negative Social Interactions Scale [54]
Chronic stress	Cohen's Perceived Stress Scale [55]
	Karasek's Job Content Questionnaire [56]
	Siegrist's Effort-Reward Imbalance Questionnaire [57]
	Modified Dyadic Adjustment Scale [58]
	Caregiver Stress Selected Items [59]
	Williams Detroit Everyday Discrimination Scale [60]
	Perceived Ethnic Discrimination Questionnaire - Community Version [61]

Table 3
Target enrollment by sex, ethnicity, and race.

	Sex		
	Females	Males	Total
Ethnic category			
Hispanic or Latino	36	36	72
Non-Hispanic or Latino	70	69	139
All ethnic categories	106	105	211
Racial category			
American Indian/Alaskan Native	1	0	1
Asian	3	3	6
Native Hawaiian or Pacific Islander	0	0	0
Black or African American	32	32	64
White	47	47	94
More than one race	23	23	46
Unknown or not reported	0	0	0
All racial categories	106	105	211

3.4. *Experimental sessions*

3.4.1. *Controlled feeding period*

Dietary sodium and potassium intake are standardized to 4000 mg/day (165 mmol/day) and 2700 mg/day (72 mmol/day), respectively, by providing the participant a controlled diet for three days prior to the laboratory session. Isocaloric and micronutrient-controlled meals are designed and prepared by the Bionutrition Research Core (BRC) at the Irving Institute for Clinical and Translational Research at CUIMC. Participants are instructed to consume only the study food provided, and staff regularly contact participants to ensure complete consumption. The amounts of dietary sodium and potassium are representative of typical daily consumption by US adults [35].

3.4.2. *Laboratory session*

Following the controlled diet, participants attend a laboratory session in a fasting state and without having exercised for 12 h. Immediately upon arrival, the participant is asked to void their bladder and is fitted with a SpaceLabs 90227 ABPM device (SpaceLabs, Snoqualmie, WA), programmed to measure BP and heart rate every 5 min during the visit. The participant then drinks 200 milliliters (mL) of water and rests for 30 min in a seated position with arm and back support, legs uncrossed, and feet flat on the floor. At the end of this baseline period

(Time Point 1 [TP1] in Fig. 3), the participant reports their stress level using a Visual Analog Scale (VAS). Saliva and blood samples for serum and plasma, and urine from a complete void of the bladder, are collected.

The participant drinks another 200 mL of water and undergoes a 10-minute stress induction task in the same seated position. Coordinators leave the room and a study staff member previously unknown to the participant ("Stress Inducer") enters to administer two mental stress tasks: a 5-minute computer Stroop Color Test and a 5-minute verbal Mental Arithmetic Task. Tasks are conducted following a validated protocol [36,37]. At the end of the stress period (TP2 in Fig. 3), a second VAS stress rating, blood samples for serum and plasma, and all urine from a complete void are collected. A saliva sample is obtained 15 min after end of the stress induction, when the stress-induced peak in cortisol is expected to occur [38]. Finally, the participant drinks another 200 mL of water and begins a 30-minute recovery period during which they rest quietly without any stimulation. Following the recovery period, a final VAS stress rating and urine void are collected. VAS stress ratings are examined in blocks of 20 participants to ensure the efficacy of the psychological stress induction. The Stress Inducer is blinded to VAS ratings.

Blood samples are assayed for a basic metabolic panel, a lipid panel, and measurement of hemoglobin A1c. Urine samples are analyzed for albumin:creatinine ratio. Urine samples collected at all time points of the Laboratory Session are analyzed for sodium, potassium, chloride, and creatinine. Saliva, plasma, and urine samples are stored at −80 °C and will be analyzed for biological stress-related factors including salivary cortisol, plasma angiotensin-II and catecholamines (epinephrine and norepinephrine), and urinary endothelin-1 using ELISA kits from Abcam (Cambridge, MA), Abnova (Taipei, Taiwan), and R&D Systems (Minneapolis, MN), respectively.

3.4.3. Ambulatory session

Participants then begin an ambulatory session, which involves 24-hour ABPM collection, 24-hour urine collection, and EMAs. The participant is fitted with a Spacelabs ABPM device that is programmed to automatically measures BP and heart rate every 30 min throughout the 24-hour period. An ABPM device log is used to self-report sleep and awake times and periods of device removal.

The participant uses 2 containers to separately collect all urine voided during the daytime and nighttime periods, respectively. The nighttime container is used for collection if the participant wakes up during the night to urinate and for the first void upon waking the following morning, while the daytime container is used for all other collections until the end of the 24-hour period.

A total of 6 EMA ratings of perceived stress and negative affect are conducted during the daytime period: 5 EMA ratings are collected at random time points using Qualtrics survey links sent to the participant's cell phone using SMS text messaging. The EMA ratings are sent at least 1 h after the Laboratory Session, 1 h before expected sleep time, and 1 h after the previous EMA rating. A final EMA rating is collected upon completion of the Ambulatory Session the following morning. For each EMA rating, the participant is asked to immediately rate how stressed, angry/hostile, aggravated/irritated, anxious/tense/nervous, and sad/blue/depressed they feel at that moment. Following completion of the Ambulatory Session, the participant returns the ABPM device and the 2 urine containers.

4. Measures

4.1. Primary aims 1 and 2

The variables used to evaluate the primary aims will be:

(1) The change in urinary sodium excretion rate with stress (uEq/min), as measured by urinary excretion rate of sodium at baseline (TP1) and post-stress (TP2). Urinary excretion rate is calculated

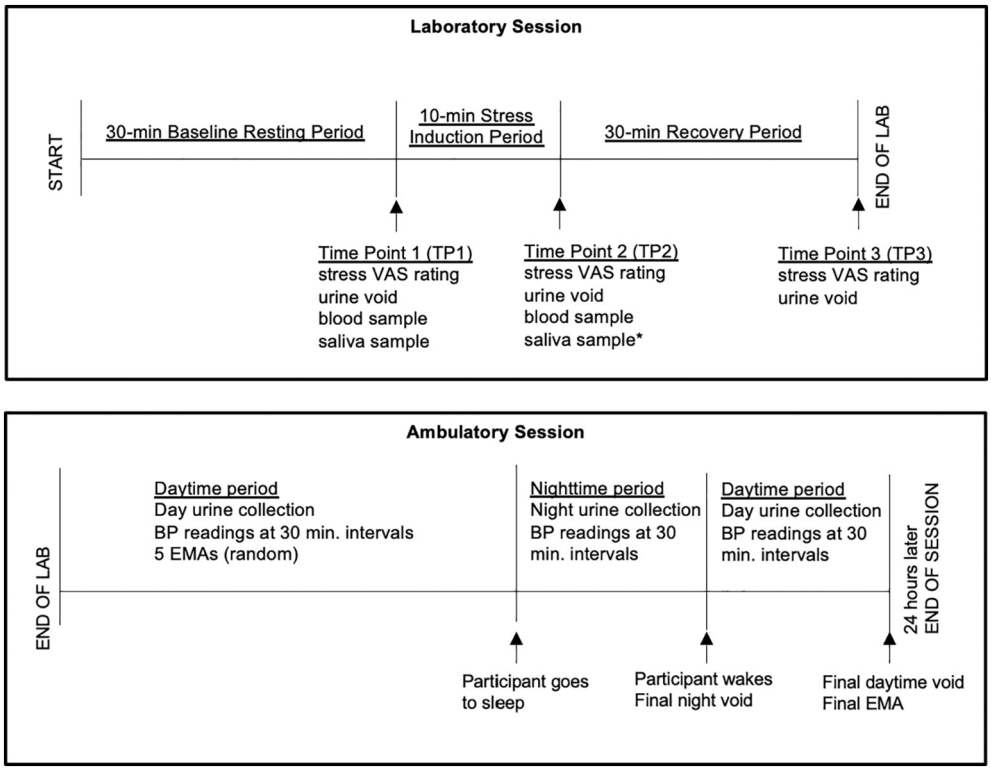

Fig. 3. Laboratory and ambulatory sessions.
*Saliva is collected 15–20 min after the stress induction period ends (to capture peak salivary cortisol levels), this collection does not occur simultaneously to the blood collection, urine collection, and stress visual analogue scale (VAS) rating at TP2.

by multiplying urinary sodium concentration (uEq/mL) by urinary flow rate (V, mL/min).

(2) The daytime-to-nighttime ratio of sodium excretion (unitless), calculated from the urinary sodium excretion rates in the daytime and nighttime containers. 24-hour sodium excretion, 24-hour potassium excretion, 24-hour creatinine clearance, and fractional excretion of sodium (FENa) are also calculated.

(3) The systolic blood pressure (SBP) dipping (%), calculated as 100 * (mean awake SBP - mean sleep SBP)/(mean awake SBP). Diastolic (DBP) dipping will be calculated similarly as a secondary measure, given its weaker association with CVD compared to SBP dipping [4,6].

4.2. Secondary aims

EMA ratings of perceived stress (e.g., how stressed the participant feels) will be used to evaluate this aim. The ecological stress level for the day period will be defined as the mean perceived stress level across the 6 EMA reports.

4.3. Exploratory aims

The study's exploratory aim will use data from the questionnaire assessments of sociodemographic, behavioral, psychological trait, chronic stress, and biological stress-related factors.

5. Statistical analyses

5.1. Primary aim 1

We will predict the daytime-to-nighttime ratio of urinary sodium excretion rate from the change in urinary sodium excretion rate with stress. In addition to an unadjusted regression model with no covariates, we have a priori selected the following covariates for adjustment in a multiple regression model: age, sex, race/ethnicity, and body mass index (BMI). The statistical significance of the coefficient for the change in urinary sodium excretion rate with stress in this adjusted model will constitute the primary test of the hypothesis. Sensitivity analyses will be performed to assess whether the strength of the association changes when additional covariates are included: office BP, parental history of hypertension, fasting glucose, and 24-hour creatinine clearance.

5.2. Primary aim 2

The same approach for Primary Aim 1 will be used for Primary Aim 2. We will predict BP dipping from the daytime-to-nighttime ratio of urinary sodium excretion rate in an unadjusted model. In an adjusted model, the following covariates were selected a priori: age, sex, race/ethnicity, BMI, 24-hour sodium excretion, 24-hour potassium excretion, 24-hour creatinine clearance, FENa, current smoking, alcohol consumption, and glucose. Sensitivity analyses will be performed after additional covariates are included in the adjusted model: physical activity and fasting glucose.

5.3. Secondary aim

EMA level of perceived stress is conceptualized as a potential moderator of the hypothesized effect of change in urinary sodium excretion rate with stress on daytime-to-nighttime ratio of sodium excretion. We will test their multiplicative interaction term while controlling for the effects of perceived stress and change in urinary sodium excretion rate with stress. This analysis will be an extension of the regression model used to test Primary Aim 1. Although a moderator is not required to be associated with the outcome, we will examine the association between mean perceived stress and daytime-to-nighttime ratio of urinary sodium excretion rate.

5.4. Exploratory aim

Univariable and multivariable linear regression analyses will be performed to assess which psychosocial, sociodemographic, biological stress-related factors are independently associated with lower stress-induced sodium excretion rate. All models will adjust for age, sex, and race/ethnicity. Given the large number of predictors being examined, we will apply a false discovery rate of 0.05 and interpret the results as "hypothesis generating" rather than "confirmatory."

The sample size was selected to ensure 80% power for the Primary Aims to detect a bivariate/partial correlation between the primary predictor and outcome of $r = 0.20$ or greater. The minimum sample size required to detect this effect size with 80% power is 194 with valid data for the measures for the Primary Aims. We are targeting a final minimum sample size with complete data of 200.

5.5. Additional exploratory analyses

Social determinants of health obtained from the questionnaires will be evaluated as candidate covariates by selecting those that are associated with the outcomes in Primary Aims 1 and 2 at $p < 0.10$. The analyses for Primary Aim 2 will be repeated using mean sleep SBP and mean sleep DBP instead of SBP dipping and DBP dipping, respectively. The analyses for the Secondary Aim will be repeated using the average of the EMA reports for each negative affect instead of perceived stress to determine whether negative affect moderates the association between lower stress-induced sodium excretion and an abnormal diurnal pattern of sodium excretion. This analysis will be repeated using a composite negative affect score derived by averaging the EMA reports of all negative affect ratings. We will evaluate multiplicative interaction terms of sex and separately race/ethnicity with (1) stress-induced sodium excretion to test for group differences in its association with the diurnal pattern of sodium excretion; and with (2) the diurnal pattern of sodium excretion to test for group differences in its association with diurnal pattern of BP.

6. Ethics & trial oversight

The Columbia University Institutional Review Board (IRB) approved this study. Informed consent and Health Insurance Portability and Accountability Act (HIPAA) Authorization for Research forms are signed at the time of participant enrollment. All research staff involved in this study have completed IRB and HIPAA training and possess the required materials and instructions for proper and ethical obtaining of consent.

7. Discussion

The goal of this study is to test a theoretical model linking diurnal patterns of sodium excretion and BP, urinary sodium excretion in response to provoked stress, and the experience of ecological levels of stress to increase our understanding of the mechanisms underlying reduced BP dipping. By examining the sociodemographic, behavioral, psychological trait, chronic stress, and biological stress related factors that are associated with lower stress-induced sodium excretion, the SABRE study will also identify factors associated with lower stress-induced sodium excretion and reduced BP dipping.

Our study addresses part of a compelling question: what are the pathways underlying the effects of diurnal patterns on health? The conduct of mechanistic studies help identify potential treatment targets for reducing the CVD risk associated with reduced BP dipping. If confirmed, our study has exciting implications for CVD prevention. The administration of antihypertensive medications that increase sodium excretion (e.g., diuretics) might be beneficial among patients with reduced BP dipping that is due to an abnormal diurnal pattern of sodium excretion. In contrast, administration of other antihypertensive medication classes that do not influence sodium excretion (e.g., calcium

channel blockers) may not reduce the CVD risk of these individuals. Thus, our findings may enhance the use of precision medicine in the treatment of hypertension.

Finally, the study will determine the factors associated with lower stress-induced sodium excretion. These results may help identify those individuals who should be targeted for stress-induced sodium excretion testing and determine the possible etiologies underlying lower stress-induced sodium excretion. This would lay the groundwork for future mechanistic or intervention studies.

8. Limitations

There are potential limitations to the SABRE study. We do not include a neutral condition in the Laboratory Session as a control, as the purpose of this study is not to determine whether an exposure to an acute stressor using a mental stress task will increase urinary sodium excretion when compared to a neutral condition. Consistent with prior studies [19,22,23,25–30,39,40], we defined stress-induced sodium excretion as the change in urinary sodium excretion after provoked stress compared to a resting baseline, allowing for each person's resting baseline to serve as their own control. We believe this is a better approach than using a within-subjects design for which all participants undergo both the mental stress tasks and a neutral condition, which may be limited by carryover effects from one condition to the other.

Many studies that have examined stress-induced sodium excretion and the diurnal patterns of sodium excretion and BP did not standardize sodium consumption [17–21,23,28,39]. Therefore, the degree to which the reported associations between stress and salt excretion might be explained by dietary sodium intake remains unknown. To control for dietary sodium, the amount of dietary sodium and potassium is being fixed for all participants. However, since the food is provided to participants to consume at home, it is possible for them to deviate from the study diet. After completion of the SABRE study, future studies can characterize the hypothesized associations among participants who are taking different amounts of dietary sodium and potassium. Finally, a few small studies suggest that sodium sensitivity is associated with an abnormal diurnal pattern of BP and also possibly the diurnal pattern of sodium excretion [16,41–43]. Although the role of sodium sensitivity is an important consideration, determination of sodium sensitivity would require a within-subjects design for which participants are exposed to both a high and low sodium diet. The question of whether there is an interaction effect of dietary sodium and sodium sensitivity on the diurnal patterns of sodium excretion and BP should be addressed in a future study.

9. Conclusions

Evidence suggests that an abnormal diurnal pattern of BP is associated with an increased risk of CVD. The SABRE study examines urinary sodium excretion induced by psychological stress and its diurnal pattern as a novel biological mechanism that may underlie an abnormal diurnal pattern of BP. The study will test the hypotheses that lower stress-induced sodium excretion is associated with an abnormal diurnal pattern of sodium excretion, and that an abnormal diurnal pattern of sodium excretion is associated with an abnormal diurnal pattern of BP. The SABRE study addresses important knowledge gaps and limitations in the literature and does so in the context of a rigorous translational study that is conducted both in the laboratory setting and in the naturalistic environment. Further, the study population includes a multiracial/ethnic community sample. The study has high clinical significance for advancing our understanding of the role of psychological stress in human hypertension and has the potential for reducing the CVD risk associated with an abnormal diurnal pattern of BP.

Funding sources

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Registration information

Study Registration: The study is registered on ClinicalTrials.gov: NCT03636490.

Disclosures

Daichi Shimbo, MD, is a consultant for Abbott Vascular, Edward Lifesciences, Medtronic and Tryton Medical. He conducts event ascertainment for trials that they are conducting (testing coronary and valvular disease interventions). These studies are unrelated to the content area of this manuscript.

No other authors have relevant disclosures to report.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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