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Association of Estimated Sodium Intake With Adverse Cardiac Structure and Function

From the HyperGEN Study

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ABSTRACT

BACKGROUND The optimal level of sodium intake remains controversial.

OBJECTIVES This study sought to determine whether examination of left ventricular longitudinal strain (LS), circumferential strain, and e′ velocity can provide insight into thresholds for the detrimental effects of estimated sodium intake (ESI) on subclinical cardiovascular disease.

METHODS We performed speckle-tracking analysis on HyperGEN (Hypertension Genetic Epidemiology Network) study echocardiograms with available urinary sodium data (N = 2,996). We evaluated the associations among ESI and LS, circumferential strain, and e′ velocity using multivariable-adjusted linear mixed-effects models (to account for relatedness among subjects) with linear splines (spline 1: ESI ≤3.7 g/day, spline 2: ESI >3.7 g/day based on visual inspection of fractional polynomial plots of the association between ESI and indices of strain and e′ velocity). We performed mediation analysis to understand the indirect effects of systolic blood pressure and serum aldosterone on the relationship between ESI and strain and e′ velocity.

RESULTS Mean age of participants was 49 ± 14 years, 57% were female, 50% were African American, and 54% had hypertension. The median ESI was 3.73 (interquartile range: 3.24, 4.25) g/day. ESI >3.7 g/day was associated with larger left atrial and left ventricular dimensions ($p < 0.05$). After adjusting for speckle-tracking analyst, image quality, study site, age, sex, smoking status, alcohol use, daily blocks walked, diuretic use, estimated glomerular filtration rate, left ventricular mass, ejection fraction, and wall motion score index, ESI >3.7 g/day was associated with both strain parameters and e′ velocity ($p < 0.05$ for all comparisons), but ESI ≤3.7 g/day was not ($p > 0.05$ for all comparisons). There were significant interactions by potassium excretion for circumferential strain. Mediation analysis suggested that systolic blood pressure explained 14% and 20% of the indirect effects between ESI and LS and e′ velocity, respectively, whereas serum aldosterone explained 19% of the indirect effects between ESI and LS.

CONCLUSIONS ESI >3.7 g/day is associated with adverse cardiac remodeling and worse systolic strain and diastolic e′ velocity. (J Am Coll Cardiol 2017;70:715–24) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

A = late/atrial diastolic transmitral velocity

BMI = body mass index

E = early diastolic transmitral velocity

EF = ejection fraction

ESI = estimated sodium intake

IQR = interquartile range

LV = left ventricle

RAAS = renin-angiotensin-aldosterone system

STe′ = speckle-tracking e′ velocity

Only a small percentage of the world's population meets current sodium intake goals of 1.5 to 2.3 g/day (1-4). Findings from several recent studies, however, have challenged these recommendations (5-7). A large prospective cohort study showed a J-shaped relationship, whereby an estimated sodium intake (ESI) of 3 to 6 g/day resulted in the lowest risk for death and cardiovascular events (6). Conversely, longitudinal results from the TOHP (Trial of Hypertension Prevention) suggested that ESI is linearly related with mortality. Furthermore, the mechanistic underpinnings of such associations are poorly understood. For example, it has been shown that the relationship between ESI and mortality is not simply mediated by higher blood pressure, a known consequence of increased sodium intake (2,8). Because of the paucity of clinical trials dedicated to determining whether low sodium intake reduces cardiovascular events, we must rely on well-executed, observational analyses and sound biological plausibility to determine optimal sodium intake (8). Whether urinary sodium, a surrogate marker of ESI, is associated with subclinical measures of cardiac dysfunction, such as myocardial strain, remains unknown. Strain is a sensitive indicator of cardiomyocyte health that correlates with fibrosis, cardiomyocyte hypertrophy, and abnormal calcium transients within cardiomyocytes (9), and therefore it may provide insight into the relationship between ESI and cardiovascular disease.

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We thus sought to study the relationship between ESI and indices of cardiac mechanics and hypothesized that higher ESI is associated with worse systolic strain and impaired myocardial relaxation in individuals free of clinical heart failure. We leveraged the HyperGEN (Hypertension Genetic Epidemiology Network) study, a large population- and family-based study—which included overnight urine collections from which urine sodium concentrations were measured, and in which we have previously performed speckle-tracking echocardiographic analysis (10-13).

METHODS

STUDY POPULATION. HyperGEN, part of the National Institutes of Health Family Blood Pressure Program, is a cross-sectional study consisting of 5 U.S. sites, with 4 participating in an ancillary echocardiographic study (Salt Lake City, Utah; Forsyth County, North Carolina; Minneapolis, Minnesota; and Birmingham, Alabama). The goal of HyperGEN was to identify and characterize the genetic basis of familial hypertension (14). Study eligibility required a diagnosis of hypertension prior to the age of 60 and ≥1 sibling willing to participate in the study. Hypertension was defined by an average systolic blood pressure ≥140 mm Hg or an average diastolic blood pressure ≥90 mm Hg (on ≥2 separate clinic visits) or by self-reporting treatment for hypertension. A random sample of normotensive individuals who represented the source cohort from which the HyperGEN affected sibships were identified was also recruited. Individuals with a history of type 1 diabetes mellitus or severe chronic kidney disease were excluded due to the high risk of secondary forms of hypertension. All HyperGEN study participants gave written informed consent, and the HyperGEN study was approved by each study site's local institutional review board.

CLINICAL CHARACTERISTICS. Demographic, clinical, and laboratory data were collected during the initial HyperGEN visit. Height, weight, and blood pressure were measured by trained personnel using a standardized protocol. Three consecutive, seated blood pressure measurements in each arm were obtained per person, and the second and third values were averaged and used for analysis (14). Histories of myocardial infarction, transient ischemic attack, and stroke were obtained by self-report. Diabetes mellitus was defined by fasting glucose ≥126 mg/dl, use of hypoglycemic medication, or a self-reported history. Dyslipidemia was defined by use of lipid-lowering medication, low-density lipoprotein cholesterol ≥160 mg/dl, triglycerides >150 mg/dl, or high-density lipoprotein cholesterol <40 mg/dl (for men) or <50 mg/dl (for women). Obesity was defined by body mass index (BMI) ≥30 kg/m^2. Chronic kidney disease was defined by an estimated glomerular filtration rate ≤60 ml/min/1.73 m^2.

ESTIMATED SODIUM INTAKE. Urinary electrolytes were measured from overnight urine collections (15). We extrapolated 24-h urinary sodium and potassium excretion using the method of Tanaka, since this method has reported the least bias when overnight urine specimens are analyzed (16). The 24-h urinary sodium was used as a surrogate of sodium intake.

CONVENTIONAL ECHOCARDIOGRAPHY. Echocardiography (including 2-dimensional, M-mode, and Doppler imaging) was acquired on all study participants using standardized acquisition protocols and stored in analog format (high-grade, medical quality videocassette tapes) at the time of study visit (17,18). Cardiac structure and function were quantified as

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