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Association of 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.

Objective—To determine whether examination of left ventricular (LV) longitudinal and circumferential strain (LS, CS) 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 Hypertension Genetic Epidemiology study echocardiograms with available urinary sodium data (N = 2,996). We evaluated the association between ESI and LS, CS, and e′ velocity using multivariable-adjusted linear mixed effects models (to account for relatedness among subjects) with linear splines (spline 1: ESI ≤3.7g/day, spline 2: ESI >3.7g/day based upon 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 (SBP) and serum aldosterone on the relationship between ESI and strain and e′ velocity.

Results—Mean age was 49 ± 14 years, 57% were female, 50% were African American, and 54% had hypertension. The median (25^{th}–75^{th} percentile) ESI was 3.73 (3.24–4.25) g/day. ESI >3.7g/day was associated with larger left atrial and LV 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, LV mass, ejection fraction, and

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wall motion score index, ESI >3.7g/day was associated with all strain parameters and e′ velocity in ($p < 0.05$ for all comparisons), but ESI ≤3.7g/day was not ($p > 0.05$ for all comparisons). There were significant interactions by potassium excretion for CS. Mediation analysis suggested that SBP explained 14% and 20% of the indirect effects between ESI and LS and e′ velocity, respectively, while 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.

Keywords

Urinary sodium; sodium intake; strain; echocardiography

Introduction

Only a small percentage of the world's population meets current sodium intake goals of 1.5–2.3 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 3–6 g/day resulted in the lowest risk for death and cardiovascular events (6). Conversely, longitudinal results from the Trial of Hypertension Prevention (TOHP) trials 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). Since there are no published 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 may provide insight into the relationship between ESI and cardiovascular disease.

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 Hypertension Genetic Epidemiology Network (HyperGEN) 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 (FBPP), 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 mmHg or an average diastolic blood pressure ≥90 mmHg (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 a BMI ≥30 kg/m^2. Chronic kidney disease was defined by an estimated glomerular filtration rate ≤60 $ml/min/1.73m^2$.

Estimated Sodium Intake

Urinary electrolytes were measured from overnight urine collections (15). We extrapolated 24-hour 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-hour urinary sodium was used as a surrogate of sodium intake.

Conventional Echocardiography

Echocardiography (including 2D, 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 recommended by the American Society of Echocardiography (ASE) (19,20). LV ejection fraction (LVEF) was calculated using the biplane method of discs. LV mass was calculated using the linear method recommended by the ASE and indexed to body surface area. LV hypertrophy was defined by a LV mass index >95 g/m^2 in women or > 115 g/m^2 in men. Diastolic function was quantitated using early diastolic (E) and late/atrial diastolic (A) transmitral velocities, E/A ratio, isovolumic relaxation time, and E deceleration time.

Digitization of Echocardiograms and Interpretation of Image Quality

Archived echocardiograms in analog format were converted to digital format using the TIMS 2000 DICOM System (Foresight Imaging, Chelmsford, Massachusetts). Cine loops of 2–4 cardiac cycles from the parasternal short axis (papillary muscle level) and apical four chamber views were digitized at a high rate and stored offline in DICOM format. Each study was assessed for image quality by an experienced operator, blinded to all other clinical and echocardiographic data, using a 4-point scale based on the degree of endocardial border visualized (1 = 0–25%; 2 = 25%–50%; 3 = 50%–75%; 4 = 75%–100%), similar to scales used previously (21,22).

Two-Dimensional Speckle-Tracking Analysis

Digitized cine loops were analyzed using 2D wall motion tracking software (2D Cardiac Performance Analysis [CPA], TomTec v4.5, Unterschleisshein, Germany). After isolating the highest quality cardiac cycle by visual estimation, the endocardial and epicardial borders were traced at end-systole in each view. Computerized speckle-tracking analysis was performed and endocardial and epicardial border tracings were manually adjusted to optimize tracking. Indices of LV mechanics included peak longitudinal and circumferential strain, as well as average speckle-tracking derived e' (STe′) velocities. For ease of display, strain values were converted to absolute values. Lower absolute strain values, lower STe′ velocities, and higher E/STe′ ratios were used to indicate worse cardiac function. Strain and STe′ values in our study are lower than what has been reported in the literature. For strain measurements, this may be due to differences in vendor used for post-processing software (23). The relatively low frame rates of the digitized echocardiograms (~30 fps) could also lead to lower measured values of strain and e′ velocity. In addition, for STe′ velocity, the underestimation may be due measurement of average segmental e′ tissue velocity, as opposed to tissue Doppler imaging which measures peak e′ tissue velocity. Despite these limitations, we have demonstrated that correlations between strain values measured prospectively and after digitization are high, especially for longitudinal strain and STe′ velocities (10). There is high correlation between the two methods, though consistent underestimation of e′ velocity by speckle-tracking (Online Figure 1). Furthermore, we have also been able to reproduce many known associations between several cardiovascular risk factors and strain and e′ velocity (derived from analog-to-digital conversion, followed by speckle-tracking) in HyperGEN, which supports the accuracy of our methods.

Images used for speckle-tracking analysis were generally of high quality. In the parasternal short-axis and apical 4 chamber views, 84% and 96% of images had an image quality score of ≥2, respectively, indicating good image quality for the majority of myocardial segments. Data on interobserver and intraobserver reliability shows excellent intraclass correlation coefficients for speckle-tracking parameters (Online Table 1) (10,11).

Statistical Analysis

We first created fractional polynomial plots to explore the relationship between ESI and strain, STe′, and E/STe′ ratio. A change in the slope near 3.7 g/day of ESI for reduced absolute strain values was observed in each of the plots. We repeated these analyses using restricted cubic splines with 3 knots placed at the 10^{th}, 50^{th}, and 90^{th} percentiles of ESI

(Online Figure 2). Clinical characteristics, laboratory data, and both conventional echocardiographic parameters and speckle-tracking parameters were then calculated for the total cohort and stratified by ESI (≤3.7 g/day vs. >3.7 g/day). This cutpoint was chosen based upon visual inspection of the plots as well as dichotomization of the group (median ESI was 3.73 g/day, which was rounded to 3.7 g/day for ease of clinical interpretation). Continuous data are presented as mean ± standard deviation. Categorical variables are presented as a count and percentage. We compared clinical data between groups using t-tests for normally distributed continuous variables (or non-parametric equivalent when appropriate) and Chi-squared tests for categorical variables (or Fisher's exact test when appropriate).

For our primary analyses, we used regression models with linear splines (spline 1 ≤3.7 g/day, spline 2 >3.7 g/day) to determine whether ESI was associated with worse indices of strain and STe′. Significant differences between spline slopes were confirmed for each parameter using the *mkspline* command and *marginal* option in Stata ($p < 0.05$ for all comparisons). All regression analyses used linear mixed effects models to account for relatedness among HyperGEN participants. Multivariable model 1 adjusted for speckle-tracking analyst, image quality, study site (which accounts for differences in sonographers and echocardiography equipment) as fixed effects and family membership as a random effect. Additional covariates were selected using a combination of clinical relevance and association with ESI either in previous studies or the present one. The additional covariates included in our multivariable model 1 included age, sex, smoking status, alcohol use, numbers of blocks walked per day, diuretic use, estimated glomerular filtration rate, LV mass, LVEF, and wall motion score index. We repeated our analyses using fractional polynomial regression (Online Table 2). We also created multiplicative interaction terms to determine whether there were sex, race, hypertension, or potassium excretion (<2g/day vs. >2g/day) interactions with urinary sodium in their association with strain and STe′. An interaction term $P < 0.10$ in the multivariable regression model was considered significant and explored further.

Since systolic blood pressure and serum aldosterone are along the putative causal pathway between ESI and adverse strain and STe′, we performed mediation analysis to understand these indirect effects. The following models all adjusted for model 1 covariates plus: systolic blood pressure (model 2) and serum aldosterone (model 3) (2,8,24). We calculated the proportion explained by the intermediate factors as follows: $100\% \times [\text{Beta-coefficient}_{\text{model}} - \text{Beta-coefficient}_{\text{model+intermediate factor}}]/[\text{Beta-coefficient}_{\text{model}}]$ (25). We used the likelihood ratio test to determine whether the addition of the intermediary factor resulted in a statistically significant change in the model estimates.

Beta-coefficients are displayed per 1-gram increase in ESI. A 2-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Stata v.12.1 (StataCorp, College Station, Texas).

Results

Characteristics of Study Participants

Descriptive characteristics of the study sample from HyperGEN are displayed in Table 1, dichotomized by ESI. The study cohort consisted of 2996 participants. The mean age was 49±14 years, 57% were female, and 50% were African American. Comorbidities were common, and medication use reflected standard therapies used for these comorbidities. The mean blood pressure was 126 ± 21/72 ± 11 mmHg, and obesity was common (mean BMI 31 ± 7 kg/m^2, 47% obese [BMI ≥30 kg/m^2]). Laboratory results revealed largely preserved kidney function (estimated glomerular filtration rate 86 ± 20 ml/min/1.73 m^2) and a median ESI (25th–75th percentile) of 3.73 (3.24–4.25) g/day and median (25th–75th percentile) potassium intake of 1.55 (1.32–1.78) g/day. In general, participants with higher ESI were older, were more often white, more frequently had comorbidities, had higher blood pressure, and higher BMI ($p < 0.05$ for all comparisons).

Table 2 lists both the conventional and speckle-tracking echocardiographic parameters of the study participants. Average LV structure fell within normal limits (LV end-systolic volume 51 ± 22 ml; LV end-diastolic volume 129 ± 30 ml; LV mass index 83 ± 22 kg/m^2), though one-fifth had evidence of LV hypertrophy. EF was preserved (62 ± 8%) in the majority of participants. Participants with higher ESI had larger LV and left atrial dimensions and slightly lower EF ($p < 0.05$ for all comparisons).

Association of Estimated Sodium Intake with Adverse Strain and STe′

Figure 1 shows fractional polynomial plots of ESI and strain, STe′, and E/STe′ ratio, and a threshold cut-point for worse cardiac strain was identified at roughly 3.7 g/day of ESI. Results were similar when using restricted cubic splines (Online Figure 2). Therefore, 2 linear splines were created to model the subsequent relationships (spline 1 ≤3.7 g/day; spline 2 >3.7 g/day) as shown in Table 3. After adjusting for speckle-tracking analyst, image quality, study site, age, sex, smoking status, alcohol use, blocks walked per day, diuretic use, estimated glomerular filtration rate, LV mass, LVEF, and wall motion score index, ESI was associated with all strain parameters and STe′ in linear spline 2 ($p < 0.05$ for all comparisons), but not spline 1 ($p > 0.05$ for all comparisons). While an association was demonstrated between higher E/STe′ and increased ESI in spline 2 on univariate analysis, the relationship was non-significant after multivariable-adjustment. When analyzing the relationship using multivariable fractional polynomial regression for participants with ESI>3.7 g/day, results were similar (Online Table 2). Because the ESI threshold for STe′ occurred near 2.9 g/day per Figure 1 as opposed to 3.7 g/day observed in the indices of cardiac strain, we evaluated the association between ESI and STe′ using lower thresholds. No independent association between ESI and STe′ was observed until the cutpoint was increased (in increments of 0.10 g/day) from 2.9 g/day to 3.7 g/day.

On sensitivity analysis, after excluding participants on diuretics (instead of adjusting for diuretic use in the multivariable models), the association between ESI and circumferential strain for spline 2 remained present (Online Table 3). On interaction analysis, the associations between ESI and worse circumferential strain were only demonstrated in the

presence of low estimated potassium intake. There were no other interactions observed by sex, race, or history of hypertension (Online Tables 4 and 5).

Additional models, which included further adjustment for systolic blood pressure (model 2) and serum aldosterone (model 3) generally weakened, but did not eliminate most of the observed associations observed for spline 2 and strain and STe′ (Table 4). Mediation analysis suggested that systolic blood pressure explained 14%, and 20% of the indirect effects between ESI and longitudinal strain and STe′, respectively, while serum aldosterone explained 19% of the indirect effects between ESI and longitudinal strain. We stratified the serum aldosterone analysis by race (Online Table 6). Serum aldosterone mediated a significant proportion of the relationship between ESI and both LS and STe′ in African Americans. However, no statistically significant relationship on mediation analysis was observed in white participants.

Discussion

In an analysis of 2996 participants from the HyperGEN study, we found that ESI above 3.7 g/day was associated with reduced strain and STe′. Additionally, increased ESI was also associated with adverse left atrial and LV remodeling. Mediation analysis showed that systolic blood pressure and serum aldosterone explained a significant proportion of the indirect effects between ESI and several indices of strain and e′ velocity; however, adjustment for blood pressure or serum aldosterone did not eliminate these associations. A notable proportion of the relationship remained unexplained, and this may be due to a higher proportion of individuals with cardiometabolic risk factors in the elevated ESI group. To our knowledge, this is the first study of ESI and strain, and our data may offer mechanistic insight into why high sodium intake is associated with worse cardiovascular outcomes, including heart failure (7).

On interaction testing, we found that the association between ESI and worse circumferential strain was only apparent in participants with low estimated potassium intake. High potassium intake has been shown to counteract the effects of high sodium intake in spontaneously hypertensive rats (26). Additionally, in a randomized trial of potassium intake in veterans, potassium-enriched salt compared to regular salt decreased the risk of cardiovascular death (27). Notably, we did not observe other interactions by sex, race, or history of hypertension.

In our study, elevated ESI could either drive the association with adverse strain and STe′, or it may be a marker of a higher risk patient with poor dietary habits in general. If causal, elevated ESI may be multifactorially related to worse systolic strain and impaired diastolic relaxation (Central Illustration). In animal models, salt loading has been shown to increase not only blood pressure, but also myocardial fibrosis (28,29), which could lead to progressive decrement in strain and STe′. In addition, aldosterone excess acts synergistically with high sodium diets to accelerate myocardial fibrosis. As such, aldosterone may be a potent mediator of this relationship, as demonstrated in our study as well (30–32). Furthermore, human data from a crossover trial of young men randomized to salt tablets showed salt loading induced both (1) vascular endothelial dysfunction, demonstrated by

impaired endothelium-dependent vasodilatory responses to acetylcholine, and (2) left ventricular diastolic dysfunction, possibly due to increased intracellular calcium with subsequent impaired myocardial relaxation (33). Notably, normal cardiac strain is dependent upon healthy endothelial function (34). Finally, high salt could result in increased arterial stiffness (35) which could lead to a larger reflected arterial waves that may progressively injure the myocardium. It is notable that ESI was not associated with E/e′ on multivariable analysis. We speculate that since E/e′ reflects LV filling pressures, the deleterious effects of sodium intake might first affect subclinical markers of myocardial dysfunction (strain and e′), while elevation in filling pressures may occur later in the trajectory toward HF development.

Despite numerous observational studies and several clinical trials, the optimal level of sodium intake remains unclear. This is in part due to conflicting data depending on the endpoint used (i.e. blood pressure or cardiovascular events). The Prospective Urban Rural Epidemiology (PURE) study showed that, compared to a sodium intake <3 g/day, sodium intake >5g/day was associated with the highest risk of increasing systolic and diastolic blood pressure, while only modest effects were seen at sodium intake levels between 3 and 5 g/day. In the Dietary Approaches to Stop Hypertension (DASH) trial, participants were provided meals over 30 days to accomplish moderate (3.3 g/day), low (2.5 g/day), and very low (1.5 g/day) levels of sodium intake. Low and very low levels of sodium intake reduced blood pressure significantly, though the short-term duration of the study precluded data on long-term morbidity and mortality risk (36).

However, the competing risk of renin-angiotensin-aldosterone system (RAAS) activation has led to the belief that low levels of sodium intake (<3 g/day) are also likely detrimental (37). Indeed, the PURE study also demonstrated that low ESI was associated with higher risk for cardiovascular events and mortality, though observational follow-up data from the TOHP trials showed the effect between ESI and outcomes is linear. Therefore the optimal level of sodium remains unclear. To balance the potential risk of RAAS activation at low sodium intake levels with elevated blood pressure at high sodium intake levels, some have advocated a goal sodium intake of 3–4 g/day (8). We show in this analysis that strain appears to decrease roughly around 3.7 g/day, which supports this viewpoint. These findings are significant, since only a small fraction of patients reach more conservative goals. Practically, since the majority of sodium is consumed through packaged and processed foods, low sodium dietary intake has been difficult to achieve (8). For instance, in the InterMAP study, the mean sodium intake was >3 g/day for women and >4 g/day for men in the United States; globally, sodium intake averages roughly 4 g/day (38). Additionally, in TOHP-II, the intervention group (randomized to sodium intake <1.8 g/day) only achieved a mean ESI of 2.5 g/day by 6 months and 3.1 g/day by 36 months (39). Therefore, long-term reduction in sodium intake to low levels is difficult to achieve even in a clinical trial setting. Nevertheless, future clinical trials of lowering sodium intake could use speckle-tracking echocardiography as an intermediate endpoint to examine the causal relationship between lowering ESI to < 3–4 g/day and improvement in strain and STe′.

Strengths of our study include the large number of participants and comprehensive adjustment for several potential confounders, the inclusion of a large number of African

Americans, and the novel measurement of myocardial strain with speckle-tracking echocardiography to understand the mechanism between ESI and adverse cardiovascular events. Certain limitations should be considered when interpreting our results. First, sodium intake was estimated using overnight urine samples, while 24-hour urine collection is considered the gold standard. However, such testing is not feasible in large epidemiologic studies, such as HyperGEN, given challenges with compliance (8). Next, due to the cross-sectional nature of our study, we were unable establish causality. Additionally, previous studies have suggested J-shaped relationships between ESI and cardiovascular events. Indeed, low sodium may lead to excess RAAS activation with resultant detrimental physiologic effects (37). However, very few participants had a low level of estimated urinary sodium excretion (<2 g/day), and thus we were underpowered to detect such a relationship.

Conclusions

In summary, in one of the largest speckle-tracking studies to date and the first to examine the relationship between ESI (derived from measured urinary sodium values) and strain, we found that an ESI of >3.7 g/day was associated with adverse strain and STe′. Systolic blood pressure and serum aldosterone explained a significant proportion of the indirect effects between ESI and strain and STe′. These data provide support for the adverse cardiovascular effects (including direct myocardial effects) of high sodium intake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

EF	Ejection Fraction
ESI	Estimated Sodium Intake
LV	Left Ventricle
RAAS	Renin-Angiotensin-Aldosterone System
STe′	Speckle-Tracking e′ Velocity

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PERSPECTIVES

Competency in Medical Knowledge

Daily sodium intake more than 3.7 g is associated with abnormal cardiac mechanics, but this relationship is mediated only partially by systolic blood pressure and serum aldosterone levels.

Translational Outlook

Future studies should investigate the mechanism by which dietary sodium impairs myocardial function and seek therapeutic interventions that favorably influence clinical outcomes.

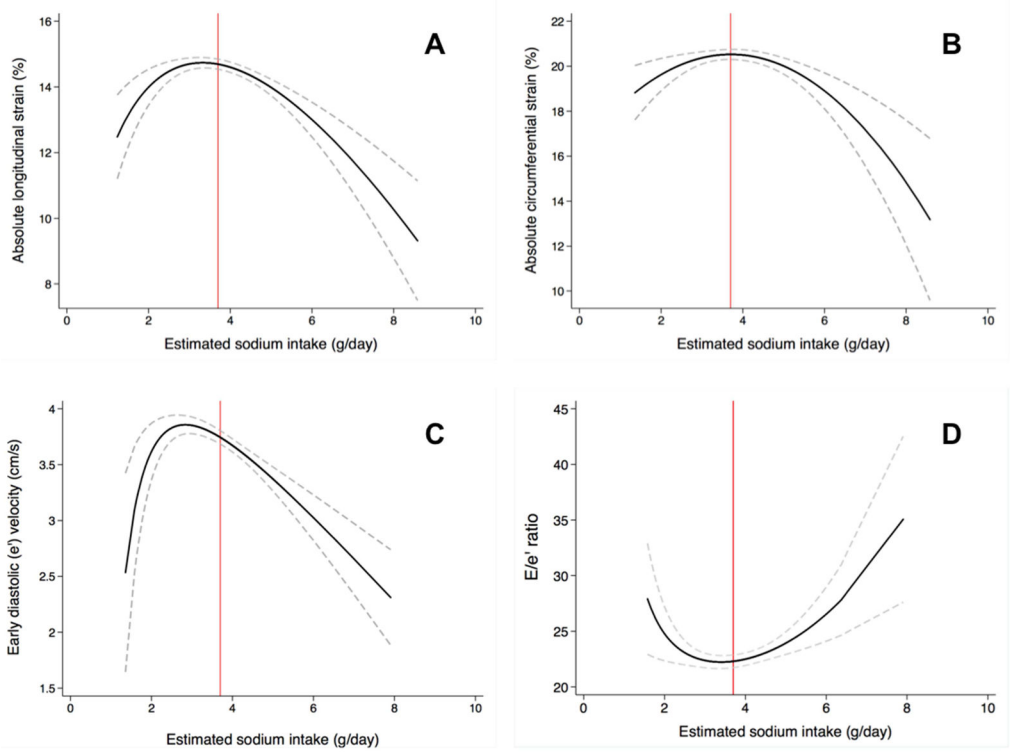
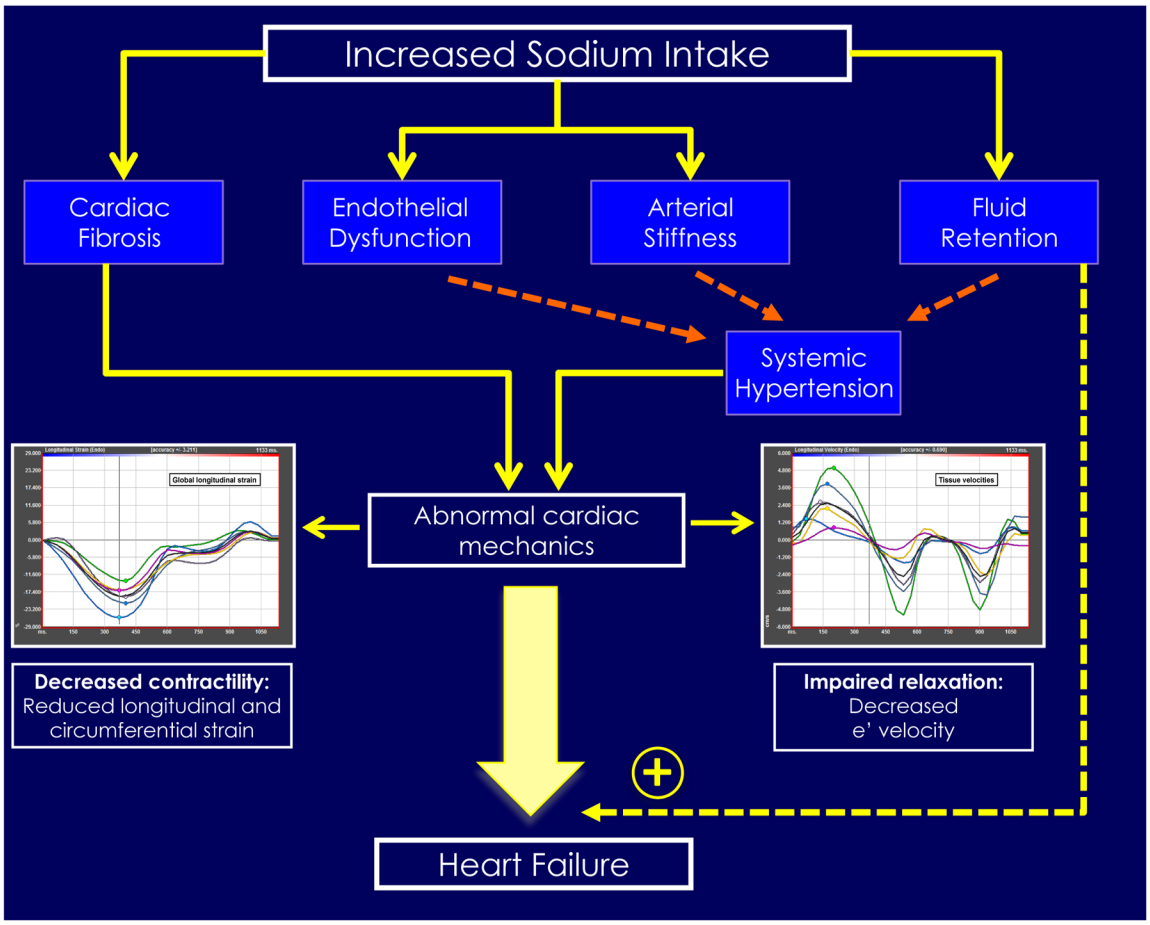


Figure 1. Unadjusted fractional polynomial plots of estimated urinary sodium excretion and strain, e′ velocity, and E/e′ ratio

(A) longitudinal strain, (B) circumferential strain, (C) early diastolic (e′) velocity, and (D) E/e′ ratio. A reference line is drawn at an estimated sodium intake value of 3.7 g/day. The 95% confidence intervals are noted by dashed lines. Plots are shown for the unadjusted relationship. Note: Tissue velocity values derived from speckle-tracking software are lower than values derived from tissue Doppler imaging. Thus, e′ is lower and E/e′ is higher in the present study compared to other studies that use conventional tissue Doppler imaging to measure tissue velocities.



Central Illustration. Urinary Sodium and Cardiac Mechanics: Estimated Sodium Intake and Adverse Cardiac Structure and Function as well as heart failure

Increased sodium intake has been associated with cardiac fibrosis, endothelial dysfunction, and arterial stiffness, which can lead to systemic hypertension. Together, these derangements may lead to adverse myocardial strain and e′ velocity as detected by speckle-tracking echocardiography in our study. In addition, increased sodium intake increases fluid retention, and when coupled with adverse strain and e′ velocity, may predispose individuals to heart failure.

Table 1

Clinical, Physical, and Laboratory Characteristics of the 2996 HyperGEN Participants by Estimate Sodium Intake

	Estimate sodium intake			
Characteristic	**All Levels (N=2996)**	**3.7≤g/day (N=1457)**	**>3.7g/day (N=1539)**	**P-value**
Age, y	49±14	47±14	51±13	<0.001
Female, n (%)	1716 (57)	855 (59)	861 (56)	0.13
Race/Ethnicity, n (%)				<0.001
White	1476 (49)	630 (43)	846 (55)	
African-American	1512 (50)	825 (57)	687 (45)	
Other	7(1)	2 (<1)	5 (<1)	
Blocks walked per day	6 (2–12)	6 (2–12)	6 (2–12)	0.84
Comorbidities, n (%)				
Hypertension	1604 (54)	690 (47)	914 (59)	<0.001
Dyslipidemia	1780 (59)	818 (56)	962 (63)	<0.001
Obesity	1394 (47)	532 (37)	862 (56)	<0.001
Current drinking	583 (24)	308 (27)	275 (22)	0.003
Current smoking	527 (18)	296 (20)	231 (15)	<0.001
Diabetes mellitus	475 (16)	172 (12)	303 (20)	<0.001
Chronic kidney disease	226 (8)	113 (8)	113 (7)	0.66
Myocardial infarction	155 (5)	61 (4)	94 (6)	0.02
Transient ischemic attack or stroke	122 (4)	56 (4)	66 (4)	0.52
Medications, n (%)				
Anti-hypertensive medication	1363 (46)	585 (40)	778 (51)	<0.001
ACE-inhibitor	541 (18)	230 (16)	311 (20)	0.002
Angiotensin receptor blocker	64 (2)	25 (2)	39 (3)	0.13
Beta-blocker	321 (11)	137 (9)	184 (12)	0.023
Calcium channel blocker	621 (21)	265 (18)	356 (23)	0.001
Loop diuretic	169 (6)	87 (6)	82 (5)	0.45
Thiazide diuretic	358 (12)	162 (11)	196 (13)	0.17
Anti-hyperglycemic medication	288 (10)	95 (7)	193 (13)	<0.001
Statin	218 (7)	88 (6)	130 (8)	0.011
Physical examination				
Systolic blood pressure, mm Hg	126±20	123±20	128±20	<0.001
Diastolic blood pressure, mm Hg	72±11	71±11	73±11	0.003
Body-mass index, kg/m^2	31±7	29±6	32±7	<0.001
Waist circumference, cm	101±17	97±16	106±17	<0.001
Laboratory data				
Estimated GFR, ml/min/1.73m^2	87±20	86±20	87±20	0.67
Fasting glucose, mg/dl	105±42	100±36	110±47	<0.001
Low density lipoprotein, mg/dl	119±34	118±35	120±34	0.13
Urinary sodium, g/day	3.78±0.81	3.13±0.44	4.38±0.56	<0.001

	Estimate sodium intake			
Characteristic	**All Levels (N=2996)**	**3.7≤g/day (N=1457)**	**>3.7g/day (N=1539)**	**P-value**
Urinary potassium, g/day	1.58±0.35	1.45±0.30	1.70±0.36	<0.001
Aldosterone, pg/ml	8.4±7.1	8.2±7.3	8.6±7.0	0.16

ACE, angiotensin-converting enzyme inhibitor; GFR, glomerular filtration rate

Table 2

Two-Dimensional, Doppler, and Speckle-Tracking Echocardiographic Parameters of the 2996 HyperGEN Participants by Estimate Sodium Intake

	Estimate sodium intake			
Conventional echocardiographic parameter	**All Levels (N=2996)**	**3.7≤g/day (N=1457)**	**>3.7g/day (N=1539)**	**P-value**
LV end-diastolic volume, ml	129±30	125±30	133±31	<0.001
LV end-systolic volume, ml	51±22	49±22	53±22	<0.001
LV mass index, g/m^2	83±22	82±21	85±23	<0.001
LV hypertrophy, n (%)	586 (20)	261 (18)	325 (21)	0.027
Left atrial diameter, cm	3.5±0.5	3.4±0.5	3.5±0.5	<0.001
Pulse pressure/stroke volume, mL/mmHg	0.71±0.23	0.70±0.23	0.72±0.22	0.06
LV ejection fraction, %	62±8	62±8	61±8	0.03
E velocity, cm/s	74±19	75±19	73±19	0.013
A velocity, cm/s	65±18	64±18	66±18	0.003
E/A ratio	1.24±0.50	1.28±0.52	1.20±0.48	0.001
E deceleration time, ms	203±56	205±56	202±55	0.31
Isovolumic relaxation time, ms	81±17	80±16	81±18	0.008
Speckle-tracking echocardiographic parameter				
STe′, cm/s *	3.7±1.3	3.8±1.4	3.6±1.3	<0.001
E/STe′ ratio *	22.7±10.1	22.5±10.1	22.9±10.0	0.41
Circumferential strain, %	20.3±5.3	20.3±5.2	20.3±5.4	0.90
Longitudinal strain, %	14.5±3.6	14.6±3.6	14.4±3.6	0.09

LV, left ventricular; STe′, speckle-tracking derived early diastolic tissue velocity. All strain values are reported as absolute values.

* Tissue velocity values derived from speckle-tracking software are lower than values derived from tissue Doppler imaging. Thus, e′ is lower and E/e′ is higher in the present study compared to other studies that use conventional tissue Doppler imaging to measure tissue velocities.

Table 3

Association of Urinary Sodium with Systolic Strain, Early Diastolic Tissue Velocity, and Estimated LV Filling Pressure on Crude and Multivariable-adjusted Analyses

Dependent variable	Model	Estimate sodium intake ≤3.7 g/day (N=1457)		Estimate sodium intake >3.7 g/day (N=1539)	
		β-Coefficient (95% CI)	P-value	β-Coefficient (95% CI)	P-value
Longitudin al strain, %	Crude	0.28 (−0.16, 0.71)	0.21	−0.91 (−1.21, −0.60)	<0.001
	Multivariable-adjusted*	0.11 (−0.30, 0.52)	0.60	−0.42 (−0.74, −0.11)	0.009
Circumfere ntial strain, %	Crude	0.44 (−0.19, 1.08)	0.17	−0.94 (1.42, 0.47)	<0.001
	Multivariable-adjusted*	0.14 (−0.51, 0.80)	0.67	−0.52 (−1.03, −0.01)	0.045
STe′ velocity, cm/s	Crude	−0.08 (−0.25, 0.10)	0.41	−0.32 (−0.45, −0.19)	<0.001
	Multivariable-adjusted*	−0.02 (−0.17, 0.13)	0.77	−0.15 (−0.27, −0.03)	0.015
Estimated LV filling pressure (E/STe′ ratio)	Crude	−0.62 (−2.25, 1.01)	0.46	1.55 (0.22, 2.88)	0.023
	Multivariable-adjusted*	−0.76 (−2.62, 1.11)	0.43	0.92 (−0.64, 2.49)	0.25

CI, confidence interval; STe′, speckle-tracking derived early diastolic tissue velocity. All strain parameters are reported as absolute values. Beta-coefficients reflect the change in the dependent variable per 1 gram/day increase in estimated sodium intake.

*Adjusted for age, sex, smoking status, alcohol use, blocks walked per day, diuretic use, estimated glomerular filtration rate, left ventricular mass, wall motion abnormalities, ejection fraction, center, speckle-tracking analyst, and image quality.

Table 4

Association of Urinary Sodium with Systolic Strain and Early Diastolic Tissue Velocity in Participants with Estimate Sodium Intake >3.7 g/day on Mediation Analysis

Dependent variable	Model 2†			Model 3‡		
	β-Coefficient (95% CI)	P-value	Proportion Explained by Systolic Blood Pressure	β-Coefficient (95% CI)	P-value	Proportion Explained by Serum Aldosterone
Longitudinal strain, %	−0.36 (−0.68, −0.04)	0.027	14%*	−0.34 (−0.66, −0.02)	0.039	19%*
Circumferential strain, %	−0.49 (−1.00, 0.01)	0.057	6%	−0.55 (−1.07, −0.04)	0.035	−6%
STe′, cm/s	−0.12 (−0.24, −0.00)	0.048	20%*	−0.14 (−0.26, −0.02)	0.025	7%

CI, confidence interval, STe′, speckle-tracking derived early diastolic tissue velocity. All strain parameters are reported as absolute values. Beta-coefficients reflect the change in the dependent variable per 1 gram/day increase in estimated sodium intake.

All models adjusted for age, sex, smoking status, alcohol use, blocks walked per day, diuretic use, estimated glomerular filtration rate, left ventricular mass, wall motion abnormalities, ejection fraction, center, speckle-tracking analyst, and image quality.

*Statistically significant change in model with addition of intermediary factor ($p<0.05$).

†Additional adjustment for systolic blood pressure.

‡Additional adjustment for serum aldosterone.