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Clinical correlates and heritability of cardiac mechanics: The HyperGEN study

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ABSTRACT

Background: Indices of cardiac mechanics are sensitive markers of subclinical myocardial dysfunction. Improved understanding of the clinical correlates and heritability of cardiac mechanics could result in novel insight into the acquired and genetic risk factors for myocardial dysfunction. Therefore, we sought to determine the clinical correlates and heritability of indices of cardiac mechanics in whites and African Americans (AAs).
Methods: We examined 2058 participants stratified by race (1104 whites, 954 AA) in the Hypertension Genetic Epidemiology Network (HyperGEN), a population- and family-based study, and performed digitization of analog echocardiograms with subsequent speckle-tracking analysis. We used linear mixed effects models to determine the clinical correlates of indices of cardiac mechanics (longitudinal, circumferential, radial strain; early diastolic strain rate; and early diastolic tissue velocities). Heritability estimates for cardiac mechanics were calculated using maximum-likelihood variance component analyses in Sequential Oligogenic Linkage Analysis Routine (SOLAR), with adjustment for clinical and echocardiographic covariates.
Results: Several clinical characteristics and conventional echocardiographic parameters were found to be associated with speckle-tracking traits of cardiac mechanics. Male sex, blood pressure, and fasting glucose were associated with worse longitudinal strain (LS) ($P < 0.05$ for all) after multivariable adjustment. After adjustment for covariates, LS, e′ velocity, and early diastolic strain rate were found to be heritable; LS and e′ velocity had higher heritability estimates in AAs compared to whites.
Conclusions: Indices of cardiac mechanics are heritable traits even after adjustment for clinical and conventional echocardiographic correlates. These findings provide the basis for future studies of genetic determinants of these traits that may elucidate race-based differences in heart failure development.

1. Introduction

The assessment of subclinical myocardial dysfunction has advanced considerably with the advent of tissue Doppler imaging and speckle-tracking echocardiography (STE), which allow for the measurement of tissue velocities and myocardial strain, respectively [1]. These indices of cardiac mechanics are sensitive indicators of myocyte injury and dysfunction [2], and can provide novel insight into potential hereditary and acquired risk factors for abnormal cardiac function and their role in the pathogenesis of myocardial disease and adverse cardiovascular events. Indeed, we have previously reported that greater burden of comorbidities is associated with worse indices of cardiac mechanics, and low-grade albuminuria—a marker of generalized endothelial dysfunction—is also associated with abnormal cardiac mechanics [3, 4].

Cardiac structure and function are important intermediate phenotypes that mediate the transition from risk factors (such as hypertension, obesity, and diabetes) to heart failure (HF). Specifically, in a rodent model of hypertension, we have previously shown that disruption of T-tubule organization (as a consequence of increased afterload) results in abnormalities in calcium cycling due to inefficient excitation-contraction coupling, and that these changes are associated with underlying abnormalities in indices of cardiac mechanics such as myocardial strain [2]. Abnormalities in strain parameters, in turn, have been shown to be associated with adverse outcomes [5], and likely represent intrinsic myocardial functional abnormalities that precede overt HF. In addition, significant race-based heterogeneity exists in

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development of HF [6, 7]. Therefore, it is appealing to study the genetic basis of intermediate phenotypes such as cardiac mechanics in whites and African Americans (AAs) rather than the heterogeneous syndrome of HF.

We therefore sought to determine whether there is a genetic component of cardiac mechanics in whites and AAs by studying the heritability and clinical correlates of indices of cardiac mechanics. We took advantage of the Hypertension Genetic Epidemiology Network (HyperGEN) Study, a large biracial population- and family-based study that included echocardiography. We hypothesized that indices of cardiac mechanics, including tissue velocities and strain parameters, are heritable traits, even after adjusting for potential confounders, and that the genetic contributions to these traits differ by race.

2. Methods

2.1. Study population

HyperGEN, part of the National Institutes of Health Family Blood Pressure Program, is a cross-sectional study consisting of five U.S. sites, with four participating in an ancillary echocardiographic study (Salt Lake City, Utah; Forsyth County, North Carolina; Minneapolis, Minnesota; and Birmingham, Alabama). The study was approved by the participating institutional review boards' and all participants gave written informed consent. The goal of HyperGEN was to identify and characterize the genetic basis of familial hypertension; complete details of the HyperGEN study design have been reported previously [8]. Study eligibility required a diagnosis of hypertension prior to the age of 60 years and at least one sibling willing to participate in the study. Hypertension was defined by an average systolic blood pressure (BP) ≥ 140 mm Hg or an average diastolic BP ≥ 90 mm Hg (on at least 2 separate clinic visits) or by self-reported treatment for hypertension. Age-matched normotensive patients were also enrolled as control subjects. Individuals with a history of type 1 diabetes mellitus (DM) or severe chronic kidney disease were excluded from HyperGEN due to the high risk of secondary forms of hypertension. None of the HyperGEN participants had symptomatic HF at the time of study enrollment.

2.2. Demographic, clinical, and laboratory characteristics

Demographic, clinical, and laboratory data were collected during the initial HyperGEN visit. Height, weight, BP, and waist circumference were measured by trained personnel, using a study-specific research protocol. Type 2 DM was defined by fasting glucose ≥ 126 mg/dl, use of hypoglycemic medication, or a self-reported history. Coronary artery disease (CAD) was defined by a self-reported history of myocardial infarction, coronary artery bypass grafting surgery, or percutaneous coronary intervention.

2.3. Conventional echocardiography

Echocardiography (including 2D, M-mode, and Doppler imaging) was acquired as part of an ancillary study to HyperGEN using standardized acquisition protocols and stored in analog format (high grade, medical quality videocassette tapes) at the time of study visit ($N = 2234$) [9, 10]. Cardiac structure and function were quantified as recommended by the American Society of Echocardiography (ASE) [11, 12]. Left ventricular 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 [11]. Diastolic function parameters included early diastolic (E) and late/atrial diastolic (A) transmitral velocities, E/A ratio, isovolumic relaxation time, and E deceleration time.

2.4. 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, MA) as described previously [13]. Cine loops of 2–4 cardiac cycles from the parasternal short axis (papillary muscle level) and apical four-chamber views were digitized at a frame rate of 30–40 frames per second and stored offline in DICOM format. Each study was scored 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 previously described [14, 15]. Image quality was high in both the parasternal short-axis apical 4-chamber views, as described previously [16].

2.5. 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) as described previously [16]. After isolating the highest quality cardiac cycle, 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 including peak longitudinal strain (LS), peak global radial strain (GRS), peak global circumferential strain (GCS), early diastolic strain rate (SR_E), and early diastolic tissue velocities (e′ velocity, measured at the septal mitral annulus) were recorded. LV filling pressures were estimated using E/e′ ratio. For ease of display, all strain values were converted to absolute values (i.e., longitudinal and circumferential strain values were converted from negative to positive values). Lower absolute strain values, lower e′ tissue velocities, and higher E/e′ ratio were used to indicate worse cardiac function. Reproducibility and accuracy of the aforementioned measurements made using our digitization and speckle-tracking protocol were found to be high (Supplemental Tables 1 and 2) [16].

2.6. Statistical analysis

We first stratified the HyperGEN study sample by race and sex and described clinical characteristics, laboratory data, and conventional and STE-derived echocardiographic parameters. Continuous data were presented as mean ± standard deviation. Categorical variables were presented as a count and percentage. Next, in order to determine the clinical correlates of indices of cardiac mechanics in HyperGEN, we used linear mixed effects models with random intercept for each family (to account for familial relatedness among participants), stratified by race. All analyses were adjusted for speckle-tracking analyst, image quality, and study site.

To determine the heritability of indices of cardiac mechanics, we utilized a maximum-likelihood variance-components approach implemented in Sequential Oligogenic Linkage Analysis Routine (SOLAR) version 6, which parses genetic and non-genetic components of variation in a trait [17]. Heritability was estimated after adjustment for covariates, which were modeled as fixed effects, in two stepwise models as listed above. We estimated heritability of cardiac mechanics indices for the entire cohort and separately for whites and AAs. Race was removed as a covariate in race-specific analyses. Heritability estimates were obtained after adjustment for covariates in a stepwise modeling process. The first model included age, sex, race, height, weight, speckle-tracking analyst, image quality, and study site (Model 1). The second model (Model 2) included all variables in Model 1 plus LV mass, LVEF, and systolic BP.

A p-value < 0.05 was considered statistically significant. Non-genetic analyses were performed using Stata version 12.0 (StataCorp, College Station, TX) and SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Characteristics of the study participants

From an initial sample size of 2234 HyperGEN participants who were randomly selected to undergo digitization and speckle-tracking analysis, 84 were excluded due to the inability to digitize the echocardiographic images due to damaged videotapes. Due to overt LV systolic dysfunction (LVEF < 50%), 92 additional participants were excluded, leaving a sample size of $n = 2058$ for the present study (Supplemental Fig. 1). In the study sample, the mean age was 51 ± 14 years, 58% were female, and 46% were AA. The cohort was obese on average with mean body mass index (BMI) of 30.7 kg/m^2. Based on the study design, hypertension (present in 55.6% of the cohort) was common; however, BP was well controlled in the majority of the study participants with mean systolic BP (126 ± 21 mm Hg) and mean diastolic BP (72 ± 11 mm Hg). Laboratory results revealed overall preserved kidney function (estimated glomerular filtration rate 85 ± 20 ml/min/1.73 m^2). Table 1 shows baseline clinical characteristics, stratified by race and sex.

Conventional echocardiographic parameters (Supplemental Table 3) demonstrated normal LV volumes and ejection fraction in the study participants. LV hypertrophy was present in 13% of the participants consistent with the high prevalence of hypertension in the enrolled cohort (with the highest prevalence of LV hypertrophy in AA females). Speckle-tracking echocardiographic parameters demonstrated lower absolute LS in AA men and women compared to whites.

3.2. Clinical correlates of cardiac mechanics

Several clinical characteristics were associated with indices of cardiac mechanics. While there was some overlap in the clinical correlates of the various indices of cardiac mechanics, there were notable differences between the indices and between races. In race-stratified analyses (adjusted for speckle-tracking analyst, study site image quality, and familial relatedness), the following factors were significantly associated with LS in both whites and AAs: female sex, systolic BP, diastolic BP, fasting glucose, LV mass index, and LVEF (Tables 2 and 3). In addition, BMI was significantly associated with LS in whites but not in AAs. Age

Table 1
Clinical characteristics of HyperGEN participants free of exclusions.

Clinical characteristic	Whites		Blacks	
	Males $N = 526$	Females $N = 578$	Males $N = 314$	Females $N = 640$
Age, years	52.5 ± 14.1	53.1 ± 12.8	46.3 ± 13.3	47.6 ± 13.3
Coronary artery disease, n(%)	50 (9.5)	25 (4.3)	25 (8.0)	33 (5.2)
Hypertension, n(%)	277 (52.7)	299 (51.7)	183 (58.3)	385 (60.2)
Diabetes, n(%)	63 (12.0)	78 (13.5)	53 (16.9)	131 (20.5)
Stroke, n(%)	17 (3.2)	15 (2.6)	22 (7.1)	25 (3.9)
Obesity, n(%)	215 (40.9)	255 (44.1)	127 (40.4)	376 (58.8)
Chronic kidney disease, n(%)	43 (8.2)	81 (14.0)	12 (3.8)	31 (4.8)
Smoking history, n(%)	227 (43.2)	162 (28.4)	208 (66.7)	270 (42.7)
Anti-HTN medication use, n(%)	252 (48)	276 (48)	146 (47)	320 (50)
Systolic blood pressure, mm Hg	126 ± 18	122 ± 21	130 ± 19	128 ± 22
Diastolic blood pressure, mm Hg	74 ± 10	67 ± 10	76 ± 12	72 ± 10
Body-mass index, kg/m^2	29 ± 5	30 ± 7	30 ± 6	33 ± 8
GFR, ml/min/1.73 m^2	81 ± 17	76 ± 16	95 ± 21	93 ± 21
Fasting glucose, mg/dl	103 ± 28	101 ± 39	108 ± 51	108 ± 48
Total cholesterol, mg/dl	191 ± 37	201 ± 39	194 ± 42	196 ± 39
HDL cholesterol, mg/dl	42 ± 10	53 ± 15	50 ± 15	56 ± 15
Triglyceride, mg/dl	142 (99–205)	140 (95–203)	93 (68–131)	89 (64–127)
LDL cholesterol, mg/dl	116 ± 32	117 ± 34	122 ± 40	120 ± 35

GFR = glomerular filtration rate; HTN = hypertension; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

and LVEF were consistently associated with GCS in whites and AAs. Only age was significantly associated with GRS in whites and AAs. Age, SBP, fasting glucose, and LV mass index were significantly associated with e′ velocity in both whites and AAs. Age, female sex, systolic BP, fasting glucose, and LVEF were each significantly associated with SR_E in both whites and AAs.

3.3. Heritability of cardiac mechanics

Of the 2058 study participants, 2 were excluded from the heritability analyses due to missing parental data. Thus, heritability analyses were performed in 2056 participants with 1104 white participants from 486 families and 952 AA participants from 553 families. The median family size was 2 with family structure of sibships plus offspring. The range of the intra-cluster coefficient was <0.01–0.15 in AAs and 0.02–0.10 in whites. As shown in Table 4, several indices of longitudinal cardiac mechanics (LS, e′ velocity, and early diastolic strain rate) were found to be heritable traits. LS was the most heritable trait overall, with higher heritability in AAs compared to whites. In general, indices of cardiac mechanics found to be heritable remained significant after adjustment for several covariates (Model 2) with only mild attenuation of heritability estimates. GCS and GRS did not demonstrate significant heritability estimates in the overall cohort or in the race-stratified analyses. Early diastolic strain rate was only significantly heritable in whites. Inclusion of covariates can reduce the total variance while leaving the genetic component unchanged, thereby resulting in higher h2 estimates. We have therefore provided Supplemental Table 4, which displays proportion of variance due to all final covariates for indices of cardiac mechanics and ranges from 0.13 to 0.38.

4. Discussion

In this large speckle-tracking study of a population- and family-based epidemiologic study, we found that indices of longitudinal myocardial

Table 2
Clinical and conventional echocardiographic characteristics associated with indices of cardiac mechanics in African Americans.[a]

Characteristic	Absolute LS, %-units			Absolute GCS, %-units			GRS, %-units			e′ Velocity, cm/s			SR_E, 1/s		
	β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value
Age, per 10 y increase	−0.04	0.08	0.65	0.34	0.12	0.01	1.26	0.29	<0.0001	−0.51	0.03	<0.0001	−0.07	0.01	<0.0001
Female sex	−1.42	0.21	<0.0001	−1.21	0.32	0.0002	−0.62	0.76	0.42	0.09	0.10	0.34	−0.05	0.02	0.01
Hypertension	−0.88	0.21	<0.0001	0.31	0.32	0.34	0.43	0.76	0.57	−0.94	0.09	<0.0001	−0.14	0.02	<0.0001
SBP, per 10 mm Hg increase	−0.17	0.05	0.0008	−0.11	0.08	0.14	−0.11	0.18	0.55	−0.14	0.02	<0.0001	−0.03	0.00	<0.0001
DBP, per 10 mm Hg increase	−0.49	0.09	<0.0001	−0.37	0.14	0.01	0.05	0.33	0.87	−0.20	0.04	<0.0001	−0.04	0.01	<0.0001
Antihypertensive medication use	−0.64	0.21	0.003	0.41	0.31	0.20	0.70	0.75	0.34	−0.84	0.09	<0.0001	−0.13	0.02	<0.0001
BMI, per 5 kg/m^2 increase	−0.05	0.07	0.52	−0.04	0.10	0.72	−0.34	0.24	0.16	−0.03	0.03	0.36	0.00	0.01	0.58
Smoking	−0.50	0.21	0.02	−0.05	0.31	0.86	0.80	0.73	0.27	−0.28	0.09	0.003	−0.07	0.02	<0.0001
Fasting glucose, per 10 mg/dl increase	−0.06	0.02	0.01	−0.02	0.03	0.58	−0.06	0.08	0.42	−0.06	0.01	<0.0001	−0.01	0.00	0.01
LVMI, per 10 g/m^2 increase	−0.23	0.05	<0.0001	−0.16	0.08	0.05	0.08	0.19	0.69	−0.14	0.02	<0.0001	−0.03	0.00	<0.0001
LVEF, per 5% decrease	0.34	0.09	0.0003	−0.72	0.14	<0.0001	−0.23	0.33	0.49	0.08	0.04	0.07	−0.01	0.01	0.37

[a] Adjusted for speckle-tracking analyst, study site, image quality, and familial relatedness.

Table 3
Clinical and conventional echocardiographic characteristics associated with indices of cardiac mechanics in whites. [a]

Characteristic	Absolute LS, %			Absolute GCS, %			GRS, %			e′ Velocity, cm/s			SR_E, 1/s		
	β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value
Age, per 10 y increase	−0.09	0.07	0.20	0.89	0.12	<0.0001	0.71	0.28	0.01	−0.56	0.03	<0.0001	−0.06	0.01	<0.0001
Female sex	−1.18	0.18	<0.0001	−0.07	0.31	0.82	−0.41	0.73	0.58	0.16	0.08	0.07	−0.06	0.02	<0.0001
Hypertension	−0.32	0.19	0.09	1.90	0.31	<0.0001	1.36	0.75	0.07	−1.01	0.08	<0.0001	−0.12	0.01	<0.0001
SBP, per 10 mm Hg increase	−0.19	0.05	<0.0001	0.32	0.08	0.00	0.38	0.19	0.05	−0.19	0.02	<0.0001	−0.03	0.00	<0.0001
DBP, per 10 mm Hg increase	−0.49	0.09	<0.0001	0.07	0.16	0.64	0.14	0.37	0.70	−0.13	0.04	<0.0001	−0.04	0.01	<0.0001
Antihypertensive medication use	−0.01	0.19	0.97	1.96	0.31	<0.0001	1.78	0.74	0.02	−0.93	0.08	<0.0001	−0.10	0.02	<0.0001
BMI, per 5 kg/m^2 increase	−0.17	0.08	0.02	0.22	0.13	0.09	0.58	0.31	0.06	−0.18	0.04	<0.0001	−0.02	0.01	<0.0001
Smoking	0.08	0.20	0.69	−0.27	0.35	0.43	−0.38	0.82	0.64	0.06	0.09	0.55	0.00	0.02	0.86
Fasting glucose, per 10 mg/dl increase	−0.08	0.03	0.00	0.05	0.04	0.24	0.01	0.10	0.93	−0.05	0.01	<0.0001	−0.01	0.00	<0.0001
LVMI, per 10 g/m^2 increase	−0.11	0.05	0.02	0.24	0.08	<0.0001	0.24	0.18	0.17	−0.13	0.02	<0.0001	−0.02	0.00	<0.0001
LVEF, per 5% decrease	0.40	0.08	<0.0001	−0.77	0.13	<0.0001	−0.23	0.31	0.45	0.02	0.04	0.62	−0.02	0.01	<0.0001

[a] Adjusted for speckle-tracking analyst, study site, image quality, and familial relatedness.

Table 4
Heritability of cardiac mechanics.

Index of cardiac mechanics	All participants			White participants			African American participants		
	($N = 2056$)			($N = 1104$)			($N = 952$)		
	Heritability	SE	P-value	Heritability	SE	P-value	Heritability	SE	P-value
Model 1[a]									
LS	0.25	0.06	0.00001	0.22	0.07	0.0004	0.31	0.12	0.003
GCS	0.08	0.06	0.096	0.06	0.07	0.19	0.09	0.12	0.21
GRS	0.05	0.06	0.19	0.05	0.07	0.24	0.04	0.10	0.34
e′ velocity	0.25	0.07	0.00004	0.21	0.08	0.0019	0.33	0.14	0.008
SR_E	0.18	0.07	0.003	0.21	0.09	0.004	0.12	0.14	0.19
Model 2[b]									
LS	0.23	0.07	0.00006	0.20	0.07	0.0015	0.31	0.13	0.006
GCS	0.08	0.07	0.10	0.05	0.08	0.25	0.12	0.12	0.15
GRS	0.05	0.06	0.19	0.03	0.07	0.34	0.09	0.11	0.19
e′ velocity	0.25	0.07	0.00005	0.22	0.08	0.0014	0.28	0.15	0.024
SR_E	0.15	0.08	0.021	0.20	0.09	0.011	0.02	0.15	0.46

SE = standard error; LS = longitudinal strain; GCS = global circumferential strain; GRS = global radial strain; e′ = early diastolic tissue velocity at the septal mitral annulus; SR_E = early diastolic strain rate.
[a] Model 1 adjusted for age, sex, race, height, weight, speckle-tracking analyst, image quality, and study site.
[b] Model 2 adjusted for all Model 1 covariates plus LV mass, LV ejection fraction, and systolic blood pressure.

function are heritable even after adjusting for several clinical factors associated with these indices. To the best of our knowledge, ours is the first study to evaluate the heritability of indices of cardiac mechanics in AAs. We showed that LS and e′ are heritable traits with a substantial proportion of variation explained by additive genetic factors in both whites and AAs. Notably, heritability estimates were higher in AAs compared to whites.

Our findings are clinically relevant. Abnormalities in diastolic and systolic cardiac mechanics have been associated with future risk of HF and adverse cardiovascular outcomes [18, 19]. Further, lower absolute LS was shown to be associated with all-cause mortality and major adverse cardiovascular events in a meta-analysis of 5721 adults from 16 studies with a hazard ratio (per standard deviation change of LS) of 1.62 (95% CI 1.13 to 2.33, $p = 0.009$) [20]. In addition, as we have shown here and elsewhere, indices of cardiac mechanics are associated with several comorbidities and conventional echocardiographic characteristics that have been linked to HF.

Although there are several comorbidities that are associated with cardiac mechanics, considerable inter-individual variation in the development of abnormal cardiac mechanics and subclinical LV dysfunction exists. The concept of heritability allows a comparison of the relative contributions of genes and environment to variation in traits such as indices of cardiac mechanics. In our current study, narrow-sense heritability of cardiac mechanics ranged from 0.20–0.35 in fully adjusted models. These heritability estimates are on the same order as those previously reported for LV mass and e′ velocity in families of European ancestry [21]. These investigators demonstrated that LV mass, LV dimensions, and early diastolic tissue velocities are heritable traits even after adjusting for age, sex, weight, systolic BP, and heart rate. Several other studies have focused on heritability of LV mass, LV hypertrophy, left atrial size, and tissue Doppler velocities [22–25]. A recent analysis from the Framingham Heart Study, consisting of white participants, demonstrated significant heritable components for longitudinal and circumferential strain [26]. However, the average age in our HyperGEN cohort was two to three decades younger than Framingham, highlighting the importance of alterations in cardiac mechanics even earlier in the life course. This may explain a higher heritability estimate for longitudinal strain in whites in our study compared to Framingham. In addition, we also demonstrated that early diastolic strain rate has significant heritability in HyperGEN. Due to the known influences of digitization of analog echocardiograms and post-hoc speckle-tracking analysis, it is possible that an even greater proportion of the biologically meaningful component of cardiac mechanics is explained by genetic factors in HyperGEN.

Our finding that AAs had higher heritability estimates for longitudinal strain and e′ velocity may be particularly important given data showing that AAs have worse cardiac mechanics and increased susceptibility to HF. Data from the Coronary Artery Risk Development in Young Adults (CARDIA), demonstrated lowest longitudinal and circumferential strain in AA men among participants free of overt HF with a mean age of approximately 50 years old [27]. In a 20-year follow-up of the CARDIA participants, incident HF was also more common among AAs than whites [7]. Furthermore, the Multi-Ethnic Study of Atherosclerosis reported that the risk of developing HF was greater among AAs compared to whites [6]. In addition, the prevalence of HF is predicted to remain the highest among AAs, reaching 3.6% by 2030 [28]. Therefore, an understanding of race-based differences in the development of HF is important to help mitigate the epidemic of HF in AAs. In taking advantage of the family-based structure of HyperGEN, our findings suggest that AA individuals have a stronger heritable component for longitudinal parameters of systolic and diastolic function that may represent antecedents to subsequent HF.

While it is important to establish that a heritable basis for complex traits such as cardiac mechanics exist before embarking on genetic studies, limitations of heritability analysis include that it is a population and situation-specific parameter. In a genetically heterogeneous population, heritability will provide a more accurate estimate than in a genetically homogenous population. Despite well-accepted genetic contributions to cardiac structure and function, three large genome-wide association studies (GWAS) focused on LV mass and dimensions have yielded disappointing results. The EchoGEN consortium of investigators published the first large-scale GWAS of cardiac structure and function in five community-based cohorts of European descent ($n = 12{,}512$) identified only one locus (6q22), which achieved genome-wide significance, was successfully replicated, but only explained <1% of the trait variance [29].

Given the well-supported relationship of abnormal cardiac mechanics with adverse cardiovascular outcomes including incident HF, hospitalization for HF, and mortality, and the genetic predisposition to HF, efforts to define the genetic basis of variation in cardiac mechanics in individuals of both European and African ancestry are warranted [30–32]. The availability of genomic data and indices of cardiac mechanics in large community-based studies (including HyperGEN) will enable further studies to identify genetic variants that influence cardiac mechanics. In addition, next generation sequencing with whole exome and whole genome sequencing, as well as advances in epigenomics and analysis of gene-environment interactions will hopefully continue to improve our understanding of the genetics of cardiac structure and

function and subsequently, HF. Integration of genetic data with induced pluripotent stem cell (iPSC)-derived cardiomyocytes offers the opportunity to assess functional significance of candidate genes that may contribute to myocyte hypertrophy and heart failure as shown by Zhi et al. [33]. This study was novel in its approach by combining two cutting edge technologies and offers proof of concept of the use of whole exome sequencing and iPSCs as a novel platform for further functional studies.

4.1. Strengths and limitations

Strengths of the current report include the population-based design with large sample size and biracial participants, comprehensive clinical and echocardiographic phenotyping, and the availability of a family component to allow estimation of heritability. In addition, our study is one of the largest speckle-tracking echocardiography studies published to date. Limitations to the study must be acknowledged. First, digitization of analog echocardiographs with subsequent speckle-tracking analysis may have introduced noise into the data; however, ours is one of the largest studies of speckle-tracking echocardiography and cardiac mechanics to date, and any noise in the data may have led to lower estimates of heritability of measures of cardiac mechanics; therefore, it is possible that an even greater proportion of the biologically meaningful component of cardiac mechanics is explained by genetic factors. In addition, the majority of images were of adequate quality (91%), and image quality was used as a covariate in our multivariable analyses. Despite the fidelity of the analog-to-digital conversion technique, we were only able to acquire images at a frame rate of 30–40 fps. However, we were able to replicate several previously established associations between clinical and conventional echocardiographic correlates with cardiac mechanics. We have also previously published extensive data on reproducibility and validation of our digitization and speckle-tracking technique [13]. Further, Cheng et al. have also demonstrated very good to excellent reproducibility of strain measurements in the Framingham Offspring participants [34].

5. Conclusions

Indices of cardiac mechanics, particularly measures of longitudinal function such as LS, e′ velocity, and early diastolic strain rate are heritable traits, even after accounting for heritable clinical and echocardiographic covariates that are associated with these traits. Evidence of heritability of indices of cardiac mechanics provides the basis for future studies of genetic determinants of these traits in both AAs and whites.

Disclosures

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Appendix A. Supplementary data

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