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Recommended Citation

Selvaraj, Senthil; Aguilar, Frank G.; Martinez, Eva E.; Beussink, Lauren; Kim, Kwang-Youn A.; Peng, Jie; Rasmussen-Torvik, Laura; Sha, Jin; Irvin, Marguerite R.; Gu, C. Charles; Lewis, Cora E.; Hunt, Steven C.; Arnett, Donna K.; and Shah, Sanjiv J., "Association of comorbidity burden with abnormal cardiac mechanics: Findings from the HyperGEN study." *Journal of the American Heart Association*. 3, e000631. (2014).
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J Am Heart Assoc. 2014;3:e000631; originally published April 29, 2014;
doi: 10.1161/JAHA.113.000631

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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Association of Comorbidity Burden With Abnormal Cardiac Mechanics: Findings From the HyperGEN Study

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Background—Comorbidities are common in heart failure (HF), and the number of comorbidities has been associated with poor outcomes in HF patients. However, little is known about the effect of multiple comorbidities on cardiac mechanics, which could impact the pathogenesis of HF. We sought to determine the relationship between comorbidity burden and adverse cardiac mechanics.

Methods and Results—We performed speckle-tracking analysis on echocardiograms from the HyperGEN study (n=2150). Global longitudinal, circumferential, and radial strain, and early diastolic (e') tissue velocities were measured. We evaluated the association between comorbidity number and cardiac mechanics using linear mixed effects models to account for relatedness among subjects. The mean age was 51 ± 14 years, 58% were female, and 47% were African American. Dyslipidemia and hypertension were the most common comorbidities (61% and 58%, respectively). After adjusting for left ventricular (LV) mass index, ejection fraction, and several potential confounders, the number of comorbidities remained associated with all indices of cardiac mechanics except global circumferential strain (eg, $\beta = -0.32$ [95% CI $-0.44, -0.20$] per 1-unit increase in number of comorbidities for global longitudinal strain; $\beta = -0.16$ [95% CI $-0.20, -0.11$] for e' velocity; $P < 0.0001$ for both comparisons). Results were similar after excluding participants with abnormal LV geometry ($P < 0.05$ for all comparisons).

Conclusions—Higher comorbidity burden is associated with worse cardiac mechanics, even in the presence of normal LV geometry. The deleterious effect of multiple comorbidities on cardiac mechanics may explain both the high comorbidity burden and adverse outcomes in patients who ultimately develop HF. (*J Am Heart Assoc.* 2014;3:e000631 doi: 10.1161/JAHA.113.000631)

Key Words: cardiac mechanics • comorbidities • echocardiography • risk factors • strain

The progression from cardiac risk factors to heart failure is typically mediated by an asymptomatic stage in which structural and/or functional left ventricular (LV) abnormalities can be discerned, highlighting a prime opportunity for both

prevention of further progression and intervention.¹ Previous studies have emphasized, in particular, the effects of cardiac and non-cardiac comorbidities on abnormal LV geometry, considered both in isolation and in concert with other comorbidities.^{2–8} The addition of comorbidities results in a progressive increase in LV mass, a major risk factor for future adverse cardiovascular events.⁹ However, prior to overt cardiac remodeling or reduced ejection fraction detected by conventional 2-dimensional (2D) echocardiography, speckle-tracking echocardiography can detect subclinical alterations in cardiac performance by examining intrinsic indices of cardiac mechanics (LV strain and tissue velocities). Understanding the link between comorbidity burden and cardiac mechanics may explain why an increasing number of comorbidities predicts hospitalization in patients with heart failure.¹⁰

The evaluation of echocardiograms from the Hypertension Genetic Epidemiology Network (HyperGEN) study permits comprehensive assessment of the relationship between comorbidities and cardiac mechanics. Strengths of the HyperGEN study for studying mechanical alterations include

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Received October 27, 2013; accepted February 27, 2014.

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a large bi-racial sample of >2000 participants, comprehensive clinical and laboratory data collection, and 2-dimensional (2D) and Doppler echocardiographic data.¹¹ Speckle-tracking analysis has now allowed for the measurement of indices of cardiac mechanics in HyperGEN.

Therefore, we sought to determine whether comorbidity burden (ie, number of comorbidities) is associated with incremental worsening of cardiac mechanics. We hypothesized that accumulation of comorbidities is associated with worse cardiac mechanics (decreased LV strain and early diastolic [e'] tissue velocities), independent of its effects on LV mass and ejection fraction and even in those with normal LV geometry.

Methods

Study Population

HyperGEN, part of the National Institutes of Health Family Blood Pressure Program (FBPP), is a cross-sectional study consisting of 5 US sites, with 4 participating in an ancillary echocardiographic study (Salt Lake City, UT; Forsyth County, NC; Minneapolis, MN; and Birmingham, AL). The goal of HyperGEN was to identify and characterize the genetic basis of familial hypertension; the complete details of the HyperGEN study design have been reported previously.¹¹ Study eligibility required a diagnosis of hypertension prior to the age of 60 and at least 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 at least 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. None of the study participants had symptomatic heart failure. 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 and Definition of Comorbidity Burden

Demographic, clinical, and laboratory data were collected during the initial HyperGEN visit. Height, weight, blood pressure, and waist circumference were measured by trained personnel, using a standardized protocol. Three sitting, upright blood pressure measurements were obtained per person and averaged; further details regarding blood pressure measurements have been previously reported.¹¹ Histories of

myocardial infarction, transient ischemic attack, or 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 body mass index ≥ 30 kg/m². Chronic kidney disease was defined by an estimated glomerular filtration rate ≤ 60 mL/min per 1.73 m².

Comorbidity burden was defined as the number of the following comorbidities: hypertension, dyslipidemia, obesity, diabetes mellitus, chronic kidney disease, coronary artery disease, and transient ischemic attack/stroke.

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.^{12,13} Cardiac structure and function were quantified as recommended by the American Society of Echocardiography (ASE).^{14,15} LV ejection fraction 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/m² in women or > 115 g/m² in men. Normal geometry was defined by the absence of LV hypertrophy. 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). Cine loops of 2 to 4 cardiac cycles from the parasternal short axis (papillary muscle level) and apical 4-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% to 25%; 2=25% to 50%; 3=50% to 75%; 4=75% to 100%), similar to scales used previously.^{16,17}

Two-Dimensional Speckle-Tracking Analysis

Digitized cine loops were analyzed using 2D wall motion tracking software (2D Cardiac Performance Analysis [CPA], TomTec v4.5). 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 included peak global longitudinal strain (GLS), peak global radial strain (GRS), peak global circumferential strain (GCS), and early diastolic (e') tissue velocities. LV filling pressures were estimated using E/e' ratio. For ease of display, all strain values were converted to absolute values (ie, 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. A validation of the digitization and speckle-tracking techniques employed here have been published elsewhere.¹⁸ Intra- and inter-observer reliability data for speckle-tracking measurements in HyperGEN were excellent, as detailed previously.¹⁹

Statistical Analysis

Clinical characteristics, laboratory data, and both conventional echocardiographic parameters and speckle-tracking parameters are displayed for the total cohort. Continuous data are presented as mean \pm standard deviation. Categorical variables are presented as a count and percentage.

We performed multivariable analyses to determine whether number of comorbidities is associated with worse indices of cardiac mechanics and increased LV filling pressure (ie, E/e' ratio) after accounting for potential confounders. We used linear mixed effects models, thereby accounting for relatedness among HyperGEN participants. Analyses were repeated after excluding participants with a prior history of myocardial infarction to determine whether number of non-cardiac comorbidities is associated with worse indices of cardiac mechanics and increased LV filling pressure. Further analyses were performed in participants with normal LV geometry.

Multivariable-adjusted logistic mixed effects models were used to determine which comorbidities predicted abnormal GLS by the ASE definition ($<12\%$).²⁰ For the outcome of abnormal GLS, we performed additional analyses to explore whether a weighted comorbidity index would perform better than equal weighting of comorbidities. We performed a logistic regression analysis with abnormal GLS ($<12\%$) as the dependent variable and individual comorbidities as the independent variables. Next, we created a weighted comorbidity index based on the model coefficients for each of the comorbidities. Finally, we compared the un-weighted comorbidity index with the weighted comorbidity index with receiver operating characteristic (ROC) analyses.

For our multivariable analyses, Model 1 included speckle-tracking analyst, image quality, and center (as well as familial relatedness, which was entered into the model as a random

effect). Model 2 included all Model 1 covariates plus age, sex, race, LV mass index, ejection fraction, and wall motion score index. We also conducted subgroup analyses with participants stratified by race and sex. Multiplicative interaction terms were created and entered into regression models to determine whether there were interactions between comorbidity burden and race/sex.

A 2-sided P value <0.05 was considered statistically significant. Analysis was performed using Stata v.12 (Stata-Corp) and SAS v. 9.0 (SAS Institute).

Results

Characteristics of Study Participants

Descriptive characteristics of the study sample from HyperGEN are displayed in Table 1. The study cohort consisted of 2150 participants, randomly sampled from all 4 participating sites, representing 1089 unique families. The mean age was 51 ± 14 years, 58% were female, 47% were African American, and 53% were white. Recruitment was relatively split among the 4 centers. Comorbidities were common; only 14% of study participants were free of comorbidities, and most participants had 1 or 2 comorbidities. Figure 1 displays the histograms of number of comorbidities, stratified by sex and race. In participants with 1 or 2 comorbidities, dyslipidemia, obesity, and hypertension were the most common risk factors. Notably, 131 (6%) of the study participants had a history of myocardial infarction, and 134 (6%) had a history of coronary revascularization (coronary artery bypass surgery, angioplasty, or stent). Medication use reflected standard therapies used in the comorbidities detailed in Table 1. Calcium channel blockers (23%) and angiotensin-converting enzyme inhibitors (21%) were the most commonly employed anti-hypertensive therapies. Blood pressure was relatively well controlled ($127\pm21/72\pm11$ mm Hg), and obesity was common (mean body mass index 31 ± 7 kg/m², 47% obese [BMI >30 kg/m²]). Laboratory results revealed preserved kidney function (estimated glomerular filtration rate 85 ± 20 mL/min per 1.73 m²) in the majority of study participants.

Table 2 lists the 2D, Doppler, and speckle-tracking echocardiographic parameters of the study participants. Average LV structure fell within normal limits (LV end-systolic volume 51 ± 23 mL; LV end-diastolic volume 130 ± 31 mL; LV mass index 85 ± 22 kg/m²), though roughly one-fifth had evidence of LV hypertrophy (22%). Global LV systolic function was preserved (ejection fraction $62\pm8\%$) in the majority of participants.

Images used for speckle-tracking analysis were generally of high quality. In the parasternal short-axis and apical 4-chamber views, 85% and 97% of images had an image quality score of ≥ 2 , respectively, indicating good image quality for the majority of myocardial segments. The values obtained for

Table 1. Clinical Characteristics of the Study Sample

Characteristic	All Study Participants (n=2150)
Age, y	51±14
Female, n (%)	1255 (58)
Race/ethnicity, n (%)	
White	1144 (53)
African-American	998 (47)
Other	8 (0.3)
Recruiting center, n (%)	
Birmingham, AL	590 (27)
Minneapolis, MN	426 (20)
Salt Lake City, UT	589 (27)
Forsyth County, NC	545 (25)
Comorbidities, n (%)	
Hypertension	1251 (58)
Dyslipidemia	1310 (61)
Obesity	1021 (47)
Diabetes mellitus	365 (17)
Chronic kidney disease	197 (9)
Myocardial infarction	131 (6)
Transient ischemic attack or stroke	97 (5)
Number of comorbidities, n (%)	
0	304 (14)
1	517 (24)
2	585 (27)
3	452 (21)
4	226 (11)
5+	66 (3)
Medications, n (%)	
Anti-hypertensive medication	1095 (51)
Angiotensin-converting enzyme inhibitor	444 (21)
Alpha blocker	168 (8)
Angiotensin receptor blocker	54 (3)
Beta-blocker	275 (13)
Calcium channel blocker	488 (23)
Loop diuretic	141 (7)
Thiazide diuretic	275 (13)
Hypoglycemic medication	226 (11)
Insulin	85 (4)
Lipid lowering medication	197 (9)
Statin	174 (8)
Physical examination	
Systolic blood pressure, mm Hg	127±21
Diastolic blood pressure, mm Hg	72±11

Continued

Table 1. Continued

Characteristic	All Study Participants (n=2150)
Body-mass index, kg/m ²	31±7
Waist circumference, cm	102±17
Laboratory data	
Sodium, mEq/L	142±3
Creatinine, mg/dL	0.98±0.32
Estimated glomerular filtration rate, mL/min per 1.73 m ²	85±20
Fasting glucose, mg/dL	106±43
Total serum cholesterol, mg/dL	196±39
High density lipoprotein, mg/dL	51±15
Low density lipoprotein, mg/dL	119±34
Triglycerides, mg/dL	140±98

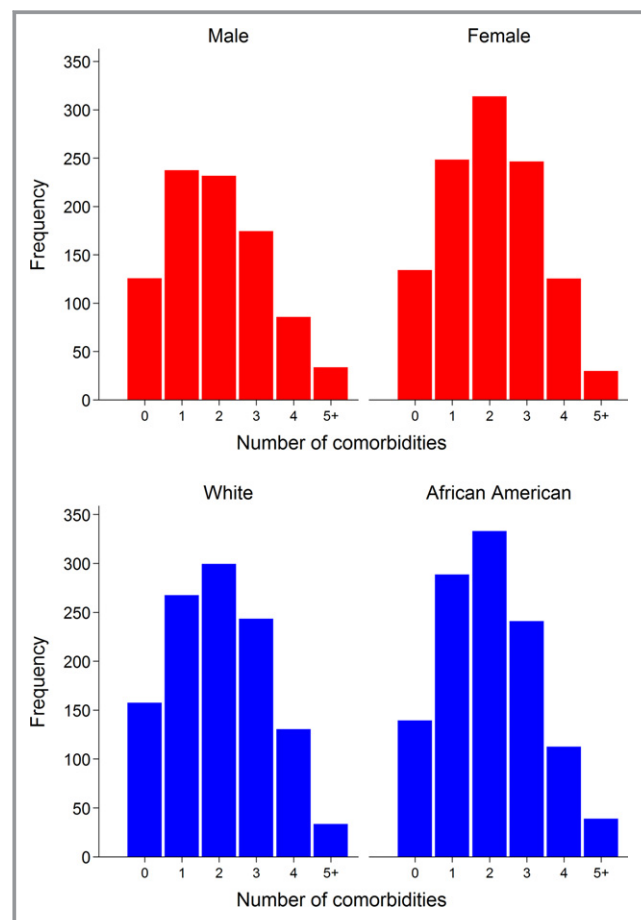
**Figure 1.** Histogram plots of number of comorbidities stratified by sex and race. Stratified by sex (top panel) and race (bottom panel). There were no significant differences in number of comorbidities by sex ($P=0.07$) or race ($P=0.58$).

Table 2. Two-Dimensional, M-Mode, Doppler, and Speckle-tracking Echocardiographic Parameters of the Study Sample

Echocardiographic Parameter	All Study Participants (n=2150)
Traditional echocardiographic parameters	
LV end-diastolic volume, mL	130±31
LV end-systolic volume, mL	51±23
LV mass index, g/m ²	85±22
LV hypertrophy, n (%)	469 (22)
Left atrial diameter, cm	3.5±0.5
LV ejection fraction, %	62±8
Stroke volume, mL	76±16
Cardiac index, L/min per m ²	2.6±0.6
Early (E) transmitral velocity, cm/s	73±20
Late/atrial (A) transmitral velocity, cm/s	66±19
E/A ratio	1.19±0.50
E deceleration time, ms	204±58
Isovolumic relaxation time, ms	80±18
Speckle-tracking echocardiographic parameters	
e' velocity, cm/s*	3.5±1.3
E/e' ratio*	23.8±11.9
Global radial strain, %	26.6±11.9
Global circumferential strain, %	20.6±5.3
Global longitudinal strain, %	14.6±3.6

LV indicates left ventricular.
*Tissue velocity values derived from speckle-tracking software are lower than values derived from tissue Doppler imaging, resulting in lower e' velocities and higher E/e' velocities.

most strain parameters were lower (ie, worse) than values obtained in patients with mild hypertension.²¹ By ASE standards, 20% had abnormally low GLS.

Association of Number of Comorbidities With Worse Cardiac Mechanics and Higher LV Filling Pressures

Figure 2 displays bar graphs demonstrating the relationship between number of comorbidities and progressively worse GLS, GCS, and GRS ($P<0.001$ for trend). Figure 3 shows a similar relationship of comorbidity burden with diastolic parameters (e' velocity and E/e' ratio) ($P<0.001$ for trend). Table 3 demonstrates the strength these associations. After adjusting for factors that could have affected the measurement of speckle-tracking parameters (Model 1; covariates=speckle-tracking analyst, recruitment center, and image quality), comorbidity burden was still associated with GLS, tissue e' velocity, and E/e' ratio ($P<0.0001$ for all

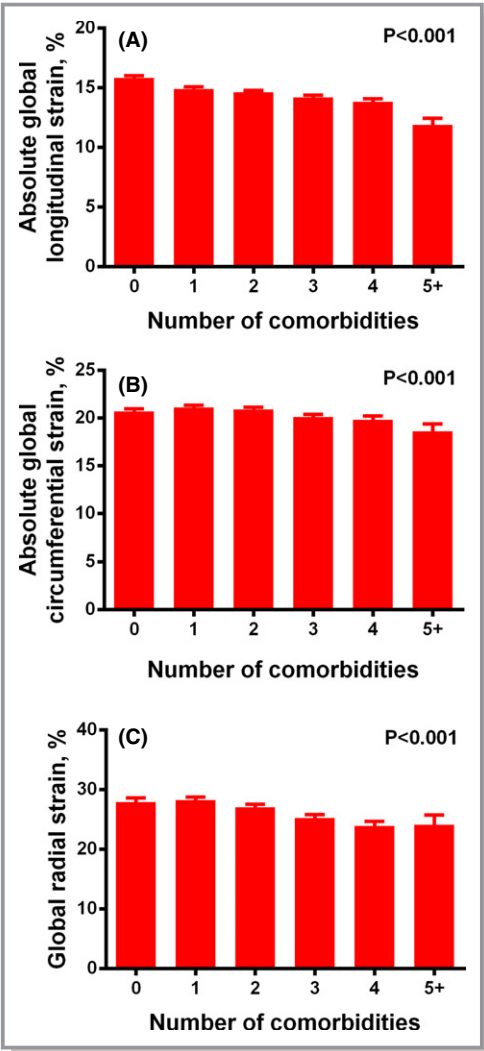


Figure 2. Bar graphs of number of comorbidities vs indices of cardiac mechanics. Increasing comorbidity burden is associated with worsening global longitudinal strain (A), global circumferential strain (B), and global radial strain (C). *P* values represent significance for the trend across number of comorbidities. Error bars represent standard errors.

associations). For instance, for each 1-unit increase in the number of comorbidities, GLS decreased by 0.41%-units. These findings were consistent in both the entire cohort and in study participants with normal LV geometry. Table 4 shows that the findings were similar even after further adjustment for additional covariates (Model 2), including age, sex, race, wall motion score index, LV mass index, and ejection fraction. Further adjustment for smoking status, systolic blood pressure, and number of anti-hypertensive medications did not attenuate the key associations between comorbidity burden and GLS ($P=0.004$), e' velocity ($P<0.0001$), and E/e' ratio ($P<0.0001$). Excluding participants with a prior history of myocardial infarction resulted in similar findings (Table 5).

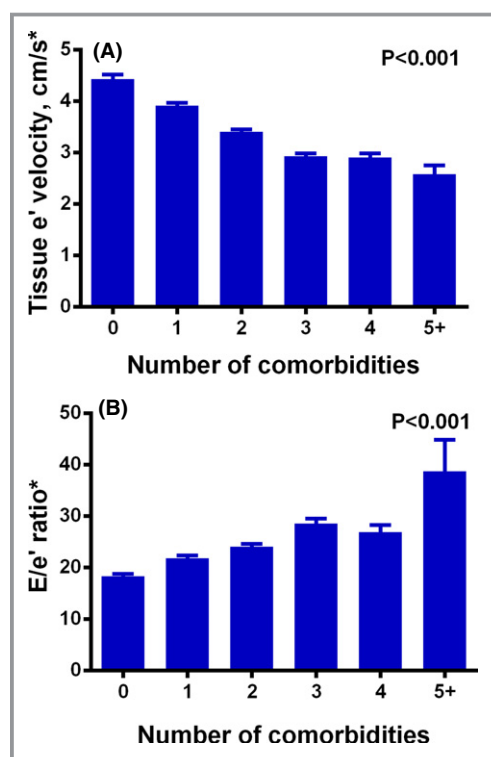


Figure 3. Bar graphs of number of comorbidities vs diastolic parameters. Increasing comorbidity burden is associated with worsening e' velocity (A) and progressively increased E/e' ratio (B), an index of increase left ventricular filling pressure. *P* values represent significance for the trend across number of comorbidities. Error bars represent standard errors. *Values for speckle tracking-derived e' velocity are lower (and therefore E/e' are higher) than those obtained clinically (via tissue Doppler imaging).

Table 6 demonstrates the association of number of comorbidities with cardiac mechanics and LV-filling pressure stratified by race/ethnicity. The effect sizes demonstrated by the beta-coefficients in Table 6 demonstrate that for every 1-unit increase in the number of comorbidities, African

Americans (compared with whites) had disproportionately worse GLS and GRS, and higher LV-filling pressure (E/e' ratio). In addition, the association of number of comorbidities with GRS was only significant in the African-American subgroup. African-American participants were more likely to be obese compared with whites (52% versus 43%, respectively). However, additional adjustment for body mass index in our multivariable models did not change the differential associations between comorbidity burden and cardiac mechanics by race. Race×comorbidities interaction testing demonstrated that there was a significant interaction ($P<0.05$) between race and comorbidity burden for GLS, GCS, and E/e' ratio (Table 6). Table 7 lists the demographic and comorbidity differences between whites and African Americans. We found no sex-based differences in the association of number of comorbidities with cardiac mechanics (interaction $P>0.10$ for all indices of cardiac mechanics).

Independent Predictors of Abnormal Global Longitudinal Strain

Table 8 displays the odds ratios for each comorbidity, as well as number of comorbidities, in predicting abnormal GLS ($<12\%$) on mixed-effects logistic regression analyses (adjusted for all factors in Model 2). After multivariable adjustment, only obesity (odds ratio 1.31 per comorbidity, $P=0.049$) and number of comorbidities (odds ratio 1.22 per comorbidity, $P=0.0009$) were independently associated with abnormal GLS. We found that a weighted comorbidity index (more weight given to those comorbidities that were more closely associated with abnormal GLS) was only slightly better than the unweighted comorbidity index (c-statistic=0.62 versus 0.61, respectively; $P=0.006$).

Discussion

In a speckle-tracking study of 2150 HyperGEN participants, we found that comorbidity burden was associated with several

Table 3. Association of Number of Comorbidities With Cardiac Mechanics and Filling Pressures After Multivariable Adjustment (Model 1)*

Dependent Variable	All Participants (n=2150)		Participants With Normal Left Ventricular Geometry (n=1620)	
	β-Coefficient (95% CI)	P Value	β-Coefficient (95% CI)	P Value
Global radial strain, %	−0.19 (−0.59, −0.20)	0.34	−0.14 (−0.60, 0.32)	0.54
Global circumferential strain, %	0.05 (−0.13, 0.22)	0.58	0.18 (−0.01, 0.39)	0.06
Global longitudinal strain, %	−0.41 (−0.52, −0.30)	<0.0001	−0.32 (−0.44, −0.19)	<0.0001
e' velocity, cm/s	−0.36 (−0.41, −0.32)	<0.0001	−0.36 (−0.41, −0.31)	<0.0001
E/e' ratio	2.69 (2.16, 3.22)	<0.0001	2.19 (1.64, 2.72)	<0.0001

*Adjusted for speckle-tracking analyst, recruiting center, image quality.

Table 4. Association of Number of Comorbidities With Cardiac Mechanics and Filling Pressures After Multivariable Adjustment (Model 2)*

Dependent Variable	All Participants (n=2150)		Participants With Normal Left Ventricular Geometry (n= 1620)	
	β -Coefficient (95% CI)	P Value	β -Coefficient (95% CI)	P Value
Global radial strain, %	−0.49 (−0.93, −0.06)	0.02	−0.52 (−1.02, −0.03)	0.04
Global circumferential strain, %	0.02 (−0.16, 0.20)	0.83	0.02 (−0.19, 0.22)	0.87
Global longitudinal strain, %	−0.32 (−0.44, −0.20)	<0.0001	−0.29 (−0.42, −0.16)	<0.0001
e' velocity, cm/s	−0.16 (−0.20, −0.11)	<0.0001	−0.15 (−0.20, −0.10)	<0.0001
E/e' ratio	1.53 (0.96, 2.11)	<0.0001	1.45 (0.86, 2.02)	<0.0001

*Adjusted for speckle-tracking analyst, recruiting center, image quality, age, sex, race, left ventricular mass index, wall motion score, and ejection fraction.

indices of abnormal cardiac mechanics and higher LV-filling pressures in a dose-response fashion. The findings were significant after controlling for LV ejection fraction and LV mass index and even in participants without evidence of LV remodeling by conventional echocardiography. To our knowledge, our study is one of the largest speckle-tracking investigations to date and is the first to show the adverse effects of comorbidity burden on intrinsic measures of myocardial function.

Our findings are clinically relevant. Based on prior studies relating GLS to outcomes, the differences in GLS across the number of comorbidities is clinically significant. Studies have shown that for every 1% worsening in GLS, the risk of adverse outcomes increases by 18% to 28%.^{22,23} Furthermore, the 4% worsening in GLS detected between participants with the lowest (0) and highest (5+) number of comorbidities has been found to be associated with an adjusted hazard ratio of 1.45 for increased mortality.²⁴

The association of comorbidity burden with worse GLS is likely explained by the vulnerability of the subendocardium. Longitudinal LV mechanics, which are largely determined by the subendocardium, are the most sensitive and vulnerable to myocardial disease processes.²⁵ Diastolic indices of impaired relaxation and increased filling pressures are likewise sensi-

tive indicators of cardiac function, which often precede overt diastolic dysfunction.²⁵ Though abnormalities in GRS and GCS, which both evaluate transmural function, often occur later in disease processes, the reason why only one (GRS) correlated well with comorbidity burden remains unclear, though the lack of association between comorbidities and GCS may have been due to the decreased accuracy of post-hoc speckle-tracking GCS compared with prospective, native GCS.¹⁸

The finding in our subgroup analysis that African Americans are disproportionately affected by comorbidity burden is particularly notable. African Americans develop heart failure at the highest incidence rate in the United States and show symptoms at early ages.^{26,27} Increased comorbidity burden has been hypothesized as one etiology.²⁶ We provide further evidence here for the role of comorbidities in disproportionate cardiac dysfunction in African-American adults. In our subgroup analyses, we found that the magnitude of the association between comorbidity burden and worse cardiac mechanics (GLS and GCS) and higher E/e' ratio was greater in African Americans compared with whites, as demonstrated by differences in effect sizes and significant interaction P values. Though African Americans develop LV hypertrophy more commonly than whites,²⁸ our analyses, which controlled for

Table 5. Association of Number of Comorbidities With Cardiac Mechanics and Filling Pressures After Multivariable Adjustment—Excluding Participants With Prior Myocardial Infarction (Model 2)*

Dependent Variable	All Participants (n=2019)		Participants With Normal Left Ventricular Geometry (n=1551)	
	β -Coefficient (95% CI)	P Value	β -Coefficient (95% CI)	P Value
Global radial strain, %	−0.46 (−0.91, −0.00)	0.048	−0.46 (−0.96, 0.5)	0.08
Global circumferential strain, %	0.04 (−0.15, 0.23)	0.68	0.04 (−0.17, 0.25)	0.69
Global longitudinal strain, %	−0.33 (−0.45, −0.21)	<0.0001	−0.29 (−0.43, −0.16)	<0.0001
e' velocity, cm/s	−0.16 (−0.21, −0.12)	<0.0001	−0.16 (−0.21, −0.11)	<0.001
E/e' ratio	1.60 (1.01, 2.18)	<0.0001	1.54 (0.95, 2.13)	<0.0001

*Adjusted for speckle-tracking analyst, recruiting center, image quality, age, sex, left ventricular mass index, wall motion score, and ejection fraction.

Table 6. Association of Number of Comorbidities With Cardiac Mechanics and Filling Pressures After Multivariable Adjustment (Model 2)—Race-Stratified Analyses*

Dependent Variable	White Participants (n=1144)		African American Participants (n=998)		Race×Comorbidities Interaction P Value
	β-Coefficient (95% CI)	P Value	β-Coefficient (95% CI)	P Value	
Global radial strain, %	−0.23 (−0.86, 0.40)	0.48	−0.69 (−1.29, −0.09)	0.025	0.44
Global circumferential strain, %	0.11 (−0.15, 0.36)	0.43	−0.12 (−0.38, 0.13)	0.34	0.003
Global longitudinal strain, %	−0.23 (−0.39, −0.07)	0.005	−0.39 (−0.57, −0.21)	<0.0001	0.026
e' velocity, cm/s	−0.16 (−0.22, −0.10)	<0.0001	−0.16 (−0.22, −0.09)	<0.0001	0.79
E/e' ratio	1.26 (0.61, 1.92)	<0.0001	1.95 (0.99, 2.91)	<0.0001	<0.001

*Adjusted for speckle-tracking analyst, recruiting center, image quality, age, sex, left ventricular mass index, wall motion score, and ejection fraction.

LV mass index, show that intrinsic inequalities in myocardial mechanics related to comorbidity burden may also play a role in the racial disparities in heart failure development and

Table 7. Differences in Demographics and Comorbidities Between White and African American Participants

Characteristic	White Participants (n=1144)	African American Participants (n=998)	P Value
Age, y	54±13	48±13	<0.001
Female, n (%)	588 (51)	660 (66)	<0.001
Recruiting center, n (%)			<0.001
Birmingham, AL	3 (<1)	587 (59)	
Minneapolis, MN	425 (37)	0 (0)	
Forsyth County, NC	584 (51)	0 (0)	
Salt Lake City, UT	132 (12)	411 (41)	
Number of comorbidities, n (%)			0.43
0	172 (15)	131 (13)	
1	267 (23)	247 (25)	
2	299 (26)	285 (29)	
3	243 (21)	206 (21)	
4	130 (11)	96 (10)	
5+	33 (3)	33 (3)	
Average number of comorbidities	2.0±1.3	2.0±1.3	0.58
Individual comorbidities, n (%)			
Hypertension	624 (55)	620 (63)	<0.001
Dyslipidemia	798 (70)	507 (51)	<0.001
Obesity	494 (43)	523 (52)	<0.001
Diabetes mellitus	160 (14)	205 (21)	<0.001
Chronic kidney disease	141 (12)	56 (6)	<0.001
Myocardial infarction	74 (6)	57 (6)	0.46
Transient ischemic attack or stroke	38 (3)	58 (6)	0.005

severity. The results shown in Table 7 suggest that race/ethnic differences in the pattern of comorbidities may also play a role in the greater role of comorbidities on cardiac mechanics in African Americans.

We found that obesity and the number of comorbidities significantly predicted abnormal GLS. Obesity has been previously implicated as a substantial risk factor for LV remodeling, and thus its relationship to GLS is not surprising.^{3,29} Previous studies have shown that individual comorbidities are associated with worse myocardial mechanics.³⁰ However, to our knowledge, ours is the first to comprehensively quantitate the adverse effects of comorbidity burden. Understanding the relationship between comorbidity burden, in addition to individual comorbidities, and cardiac mechanics is particularly clinically relevant, given the high number of patients with multiple comorbidities. Determination of cardiac mechanics may be a more sensitive and useful assay for cardiovascular prevention. Further, our results demonstrate the potential utility of examining the total number of comorbidities in the cardiac assessment of patients, since

Table 8. Predictors of Abnormal Global Longitudinal Strain by Comorbidity*

Comorbidity	Odds Ratio (95% CI)	P Value
Hypertension	1.35 (0.98, 1.85)	0.07
Dyslipidemia	1.21 (0.91, 1.59)	0.18
Obesity	1.31 (1.00, 1.72)	0.049
Diabetes mellitus	1.19 (0.85, 1.67)	0.32
Chronic kidney disease	1.52 (0.95, 2.43)	0.08
Myocardial infarction	1.42 (0.84, 2.39)	0.19
Transient ischemic attack or stroke	1.63 (0.92, 2.84)	0.08
Number of comorbidities	1.22 (1.08, 1.37)	0.0009

*Abnormal global longitudinal strain defined as <12% (see text for details); Multivariable mixed-effects logistic regression models were adjusted for speckle-tracking analyst, recruiting center, image quality, age, sex, race, left ventricular mass index, wall motion score, and ejection fraction.

the number of comorbidities was the only significant predictor of abnormal GLS apart from obesity.

Interest in the role of comorbidities in cardiovascular disease, specifically heart failure, is growing. The number of comorbidities has recently been shown to predict heart failure hospitalization, all-cause hospitalization, and death, particularly in those with preserved ejection fraction.^{10,31} Of note, a substantial percentage of patients with heart failure, regardless of ejection fraction, do not have evidence of antecedent LV hypertrophy. The reduction in indices of cardiac mechanics in participants with normal LV geometry observed in our study may underlie this transition from multiple comorbidities to the heart failure syndrome in the presence and absence of overt LV remodeling.

The importance of worsening cardiac mechanics to cardiovascular disease cannot be overemphasized. Changes in tissue deformation often precede alterations observed in traditional 2-dimensional echocardiography. Thus, a “normal” echocardiogram may not be as reassuring in the context of abnormal cardiac mechanics. In addition, GLS, in particular, is an independent predictor of all-cause mortality and is superior to conventional echocardiographic indices such as the ejection fraction or wall motion score index.²⁴ Though still an emerging tool in cardiovascular imaging, speckle-tracking echocardiography may highlight the highest risk individuals, including those with high comorbidity burden.

Our results should be interpreted in the context of a few limitations. First, the cross-sectional design of our study precludes our ability to determine whether the reductions in cardiac mechanics as a consequence of comorbidity burden result in adverse outcomes. Second, some of the comorbidities were obtained only by self-reported history. Third, speckle-tracking was performed on archival echocardiograms stored on videotapes that may have degraded image quality.²⁵ However, the vast majority of images acquired were of good or high quality; in addition, image quality was entered into all regression analyses. Fourth, we were unable to adjust for preload in our analyses, which may influence cardiac mechanics, since this echocardiographic data is not available in HyperGEN. Finally, the definition of abnormal GLS was based off measurements using a different software package, EchoPAC. However, there is low inter-platform variability when compared with TomTec speckle-tracking software.³²

In conclusion, comorbidity burden is associated with a worse cardiac mechanics and higher LV-filling pressures in a dose-response fashion, even in those with normal LV geometry and particularly in African Americans. Obesity and the number of comorbidities are significantly associated with the presence of abnormal strain. The deleterious effect of multiple comorbidities on cardiac mechanics may explain both the high comorbidity burden and adverse outcomes in patients who ultimately develop heart failure. Whether treatment of

comorbidities improves cardiac mechanics and/or outcomes should be evaluated prospectively.

Sources of Funding

The HyperGEN cardiac mechanics ancillary study was funded by the National Institutes of Health (R01 HL 107577 to Shah). The HyperGEN parent study was funded by cooperative agreements (U10) with the National Heart, Lung, and Blood Institute: HL54471, HL54472, HL54473, HL54495, HL54496, HL54497, HL54509, HL54515.

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Network Center/University of Utah Field Center: Steven C. Hunt, Roger R. Williams, Hilary Coon, Paul N. Hopkins, Janet Hood, Lily Wu, Jan Skuppin; University of Alabama at Birmingham Field Center: Albert Oberman, Cora E. Lewis, Michael T. Weaver, Phillip Johnson, Susan Walker, Christie Oden; Boston University/Framingham Field Center: R. Curtis Ellison, Richard H. Myers, Yuqing Zhang, Luc Djoussé, Jemma B. Wilk, Greta Lee Splansky; University of Minnesota Field Center: Donna Arnett, Aaron R. Folsom, Mike Miller, Jim Pankow, Gregory Feitl, Barb Lux; University of North Carolina Field Center: Gerardo Heiss, Barry I. Freedman, Kari North, Kathryn Rose, Amy Haire; Data Coordinating Center, Washington University: D.C. Rao, Michael A. Province, Ingrid B. Borecki, Avril Adelman, Derek Morgan, Karen Schwander, David Lehner, Aldi Kraja, Stephen Mandel; Central Biochemistry Laboratory, University of Minnesota: John H. Eckfeldt, Catherine Leiendecker-Foster, Ronald C. McGlennen, Greg Rynders, Michael Y. Tsai, Jean Bucks; Molecular Genetics Laboratory, University of Utah: Mark Leppert, Steven C. Hunt, Jean-Marc Lalouel, Robert Weiss; National Heart, Lung, and Blood Institute: Susan E. Old, Millicent Higgins, Cashell Jaquish, Martha Lundberg, Mariana Gerschenson. Echocardiographic reading center, Weill Cornell Medical College: Richard B. Devereux, Giovanni de Simone, Jonathan N. Bella.

Disclosures

None.

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