Cardiometabolic Traits and Systolic Mechanics in the Community

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Background—Obesity and cardiometabolic dysfunction are associated with increased risk of heart failure and other cardiovascular diseases. We sought to examine the association of cardiometabolic traits with left ventricular (LV) cardiac mechanics. We hypothesized that specific obesity-related phenotypes are associated with distinct aspects of LV strain.

Methods and Results—We evaluated the associations of obesity-related phenotypes, including central adiposity, diabetes mellitus, insulin resistance, and circulating adipokine concentrations with echocardiographic measures of LV mechanical function among participants of the Framingham Heart Study Offspring and Third Generation cohorts. Among 6231 participants, the mean age was 51±16 years, and 54% were women. Greater body mass index was associated with worse LV longitudinal strain, radial strain (apical view), and longitudinal synchrony (multivariable-adjusted \( P<0.0001 \)). After accounting for body mass index, we found that central adiposity, as measured by waist circumference, was associated with worse global longitudinal strain and synchrony (\( P≤0.006 \)). Measures of insulin resistance, dyslipidemia, and diabetes mellitus also were associated with distinct aspects of LV mechanical function. Circulating leptin concentrations were associated with global longitudinal and radial strain (apical view, \( P<0.0001 \)), whereas no such association was found with leptin receptor, adiponectin, or C-reactive protein.

Conclusions—Our findings highlight the association of central obesity and related cardiometabolic phenotypes above and beyond body mass index with subclinical measures of LV mechanical function. Interestingly, obesity-related traits were associated with distinct aspects of LV mechanics, underscoring potential differential effects along specific LV planes of deformation. These findings may shed light onto obesity-related cardiac remodeling and heart failure. (Circ Heart Fail. 2017;10:e003536. DOI: 10.1161/CIRCHEARTFAILURE.116.003536.)

Key Words: adipokine ▪ echocardiography ▪ epidemiology ▪ left ventricular function ▪ obesity

More than 1 in 4 adults are obese in the United States, and more than half of the population is projected to be obese by 2030. Obesity and metabolic disease are closely related, and both represent major risk factors for cardiovascular disease, including heart failure. Moreover, subclinical changes in cardiac structure and function are apparent in cardiometabolic disease and may precede the future development of heart failure among obese individuals. The underlying mechanisms driving cardiac remodeling in obesity are likely multifaceted and include systemic inflammation and cardiac fibrosis. Obesity may also have direct myocardial effects via circulating adipose-derived hormones such as adiponectin and leptin, which in turn have been linked to clinical heart failure.

See Editorial by Vest and Patel
See Clinical Perspective

Advanced echocardiographic imaging techniques have enabled the assessment of subclinical cardiac dysfunction. Specifically, echocardiographic strain measures have allowed for sensitive quantification of myocardial deformation and mechanics; these measures have been associated with clinical outcomes not only among patients with heart failure but also among asymptomatic community-based populations.

Received August 29, 2016; accepted March 24, 2017.
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Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.116.003536
Notably, individual components of left ventricular (LV) deformation may reflect processes affecting specific layers of myocardial fibers oriented anatomically in distinct planes. For example, shortening of the LV long axis as assessed by global longitudinal strain is thought to be a marker of predominantly subendocardial dysfunction, whereas decrease in circumferential strain around the LV short axis is considered a greater reflection of mesomyocardial dysfunction. Importantly, it is clear that there are many different facets to obesity that are manifest in phenotypes such as central adiposity, diabetes mellitus, insulin resistance, dyslipidemia, and abnormal fasting glucose. Given their complementary nature, we hypothesized that specific obesity-related phenotypes are associated with distinct aspects of LV strain. We, therefore, sought to evaluate obesity traits in relation to distinct components of LV systolic mechanics.

Methods

Study Sample
Participants of the FHS (Framingham Heart Study) offspring cohort attending the eighth examination (2005–2008) and third generation attending the first examination (2002–2005) were included in this analysis. Details of the cohorts have previously been published.16 In brief, the FHS original cohort was started in 1948 with the overall objective to identify common factors that contribute to cardiovascular disease. In 1971, the offspring cohort was recruited and included 5124 of the original participant’s adult children and their spouses. The third-generation cohort in turn included the grandchildren of the original cohort. Of 7714 eligible participants, 883 were excluded (107 because of offsite examination, 183 with prevalent myocardial infarction, 44 with heart failure, 110 with valvular heart disease, 42 with atrial fibrillation, 227 with no strain measures available, and 170 with missing covariates), leaving 6231 participants for analysis.

Clinical Assessment
At the baseline examination, a comprehensive medical history, anthropometrics, assessment of resting blood pressure, and fasting blood work were obtained. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL and antidiabetic therapy. Metabolic syndrome was defined as meeting ≥3 of 5 accepted criteria: (1) elevated waist circumference (≥102 cm in men; ≥88 cm in women); (2) increased fasting triglyceride (≥150 mg/dL); (3) high blood pressure (≥130/85 mm Hg) or treatment for hypertension; (4) decreased high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men; <50 mg/dL in women); and (5) impaired fasting glucose (≥100 mg/dL). All participants provided informed consent, and the study was approved by the Boston University Medical Center Institutional Review Board.

Laboratory Assessment
Fasting blood samples were obtained at the baseline examination and frozen at −80°C until assayed. Glucose and insulin assays have previously been described.18 The homeostasis model for insulin resistance was calculated as follows: HOMA-IR=(fasting glucose [mmol/L]×fasting insulin [μU/mL])/22.5.20 Plasma C-reactive protein concentration was measured with Dade Behring BN100 nephelometer (Dade Behring, Deerfield, IL) with intra-assay coefficient of variation of 2.8%.

On samples from third-generation participants included in this study (n=3683), plasma leptin, soluble leptin receptor, and total adiponectin concentrations were measured by ELISA (Quantikine; R&D Systems, Minneapolis, MN). Intra-assay coefficient of variations were 2.9% for leptin, 6.9% for leptin receptor, and 2.2% for adiponectin. Serum aldosterone concentration was measured via radioimmunoassay (Quest Diagnostics), and plasma renin activity was measured using the GammaCoat Plasma Renin Activity RIA Kit (DiaSorin), with interassay coefficient of variation of 12.6%.

Echocardiography
All participants underwent standard 2-dimensional transthoracic echocardiograms using an HP Sonos 5500 ultrasound machine (Phillips Medical Systems, Andover, MA). Digital echocardiographic data were analyzed offline, and conventional LV measures obtained according to standardized techniques by readers blinded to clinical data. Fractional shortening was calculated as follows: (LV end-diastolic dimension [LVDD]−LV end-systolic dimension)/LVDD × 100, and LV ejection fraction was derived using the Teichholz method.21 LV mass was calculated as follows: 0.81 × (LV posterior wall thickness+LV septal wall thickness)^2−LVDD^2)+0.65.22 LV hypertrophy was defined as LV mass >55 g/m^2 in women and >115 g/m^2 in men. Concentric hypertrophy was defined as LVH and relative wall thickness >0.42 and concentric remodeling as no LVH and relative wall thickness >0.42.

Speckle-tracking–based analyses of LV function were performed offline with excellent reproducibility as previously described (2D Cardiac Performance Analysis v1.1; TomTec Imaging Systems; Unterschleissheim, Germany).23,24 Primary measures obtained included global longitudinal strain (apical 2- and 4-chamber views), global circumferential strain (mid-LV short-axis view), and longitudinal and radial (apical) segmental synchrony, calculated as the SD of time-to-peak strain. Secondary measures included global radial strain (short-axis view) and global radial strain (apical 2- and 4-chamber views). The interobserver within-subject coefficients of variation for longitudinal and circumferential strain measures ranged from 3.0 to 4.0% and from 4.7 to 7.3% for radial strain (short-axis and apical views) as described previously.24

Statistical Analysis
Baseline clinical and echocardiographic characteristics were summarized by sex. Continuous variables that displayed skewed distributions were natural log-transformed (triglyceride concentrations, HOMA-IR, biomarkers, and measures of synchrony). The associations of cardiometabolic traits and echocardiographic measures of LV strain were evaluated using multivariable linear regression models, with a strata term used to indicate cohort. Models were adjusted for age, sex, heart rate, systolic blood pressure, hypertension treatment, body mass index (BMI), diabetes mellitus, HDL cholesterol, and triglyceride concentrations. Primary analyses examined associations of 4 cardiometabolic traits (BMI, triglyceride levels, HOMA-IR, and C-reactive protein) with longitudinal and circumferential strain. Results were deemed significant using a Bonferroni-corrected P-value threshold of 0.05/8=0.00625.

For significant multivariable-adjusted associations, secondary analyses additionally adjusted for echocardiographic measures (left atrial size, LV mass, and LV fractional shortening). We also examined other clinical traits including waist circumference, fasting glucose, HDL cholesterol, diabetes mellitus, metabolic syndrome, adiponectin, leptin, leptin receptor, and the aldosterone-to-renin ratio in secondary analyses. In an exploratory analysis, we examined age- and sex-adjusted least squares means of strain parameters grouped by number of metabolic syndrome risk factors present (ranging from 0 to 5) and assessed between-group differences using ANCOVA. In additional analyses, we examined Pearson partial correlation coefficients between traditional echocardiographic measures and speckle-track- ing measures after adjusting for age and sex. In secondary analyses, we fitted generalized linear models to further adjust primary models for sibling correlations using the GENMOD procedure in SAS. All analyses were performed using SAS v9.2.
Results

Baseline clinical and echocardiographic characteristics of 2843 men (mean age 50±15 years) and 3388 women (mean age 51±16 years) are displayed in Table 1. Among men, the mean BMI was 28.2±4.6 kg/m² and 8% had diabetes mellitus. Women had mean BMI of 26.6±6.0 kg/m², and 5% had diabetes mellitus. Baseline echocardiographic characteristics included normal mean LV ejection fraction and wall thicknesses, with 9% of the sample meeting LV hypertrophy criteria and 3% with left atrial enlargement. Mean global longitudinal strain was −19±3% in men and −21±3% in women.

Central Adiposity and Other Cardiometabolic Traits Are Associated With LV Strain

We found that higher BMI was associated with worse longitudinal and radial strain (apical). Specifically, each 1-SD increase in BMI was associated with a 0.37% higher longitudinal strain and a 0.52% lower radial strain (apical) after accounting for potential confounders, including age, sex, heart rate, HDL cholesterol, triglyceride concentrations, diabetes mellitus, systolic blood pressure, and antihypertensive therapy (multivariable-adjusted \( P<0.0001 \) for both; Table 2). A similar association with worse longitudinal and radial strain (apical) was observed with lower HDL cholesterol (\( P<0.0001 \) for both).

To examine central obesity specifically, we modeled the association of waist circumference with strain measures after adjusting for BMI among other variables (Table 2). We found that each 1-SD increase waist circumference was associated with a 0.52% higher (worse) longitudinal strain \( (P=0.006) \) and a 0.52% lower radial strain (apical) \( (P=0.007) \) after adjusting for BMI and other clinical factors. In contrast, there was no association of waist circumference and other strain measures.

Notably, higher triglyceride concentrations and insulin resistance as assessed by HOMA-IR were also associated with worse longitudinal strain (\( P<0.0001 \) for both). In addition, we found that participants with diabetes mellitus had worse circumferential and radial strain (short axis). Specifically, individuals with diabetes mellitus had a 0.84% higher circumferential and 2.91% lower radial strain (short axis) compared with individuals without diabetes mellitus (\( P≤0.004 \) for both).

After additionally accounting for traditional echocardiographic measures (left atrial diameter, LV mass, fractional shortening, or LV ejection fraction), all associations of cardiometabolic traits and strain measures highlighted above remained statistically significant \( (P≤0.007 \) for all). Additional adjustment for waist circumference and fasting glucose revealed no substantive changes in previous associations, with the exception of BMI, which was no longer associated with strain measures after adjusting for waist circumference (Table I in the Data Supplement). In secondary analyses, we accounted for sibling correlations using generalized linear models, and we found minimal differences in effect sizes (Table II in the Data Supplement).

Cardiometabolic Traits Are Associated With Mechanical Synchrony

In addition to LV strain measures, BMI was also associated with worse longitudinal segmental synchrony (multivariable-adjusted \( P=0.003 \)). After accounting for BMI and other clinical variables, waist circumference and diabetes mellitus status were also associated with worse longitudinal segmental synchrony \( (P≤0.006 \) for both; Table 3). However, after adjusting for traditional echocardiographic measures, the association...
of BMI and waist circumference with longitudinal segmental synchrony was attenuated (P>0.05 for both). There were no significant associations between cardiometabolic traits and radial (apical) segmental synchrony.

**Adipokines, Aldosterone, and LV Mechanical Function**

Higher circulating leptin concentrations were associated with worse longitudinal and radial strain (apical), even after accounting for BMI and other clinical covariates (multivariable-adjusted P<0.0001 for both; Table 3). This finding persisted even after additionally accounting for traditional echocardiographic measures (P<0.0001 for both).

Higher soluble leptin receptor concentrations were associated with higher radial strain (apical; P=0.006) but not longitudinal strain or other strain measures. Adiponectin concentrations were not associated with strain parameters (P≥0.04 for both). None of the adipokines measured were associated with synchrony measures.

We found no association of aldosterone concentrations or aldosterone-to-renin ratio and measures of LV strain. Further, the association of leptin and longitudinal and radial strain (apical) measures was not attenuated after adjusting for aldosterone concentrations in multivariable analyses (P<0.0001).

**Association of Metabolic Syndrome and Strain Measures**

Among the sample studied, 45% of men and 33% of women met criteria for metabolic syndrome. The presence of metabolic syndrome was associated with worse longitudinal and radial strain (apical) in age- and sex-adjusted analyses (P<0.0001 for both). Specifically, individuals with metabolic syndrome had a 1% higher longitudinal strain compared with those without metabolic syndrome (β estimate 1.06; SE 0.09). The Figure displays longitudinal strain by number of metabolic syndrome risk factors (between 0 and 5).

**Association of Traditional Echocardiographic Measures With Speckle-Tracking Strain**

We observed modest correlations between traditional echocardiographic measures and strain measures in age- and sex-adjusted analyses. All 4 strain measures were correlated with LV ejection fraction (Table 4). Traditional measures of diastolic function included mitral e’ velocity, with worse mitral e’ correlated with worse longitudinal strain, and the mitral inflow E/e’ ratio, with higher E/e’ ratio correlated with worse longitudinal and better circumferential strain.

**Discussion**

Among 6231 participants of the FHS, we found that greater BMI, and specifically central adiposity as measured by waist circumference, was associated with worse global longitudinal strain, as well as worse longitudinal synchrony. Beyond BMI itself, other phenotypes accompanying obesity including insulin resistance, dyslipidemia, and diabetes mellitus were associated with distinct aspects of LV mechanical function. Interestingly, we also found that the adipose-derived hormone leptin was associated with global longitudinal and radial strain (apical), whereas no such association was found with adiponectin or C-reactive protein. These findings may shed light onto obesity-related cardiac remodeling and heart failure.

The association of obesity and diastolic dysfunction is well described, whereas the effects of obesity on systolic function are less clear. Previous data support normal LV ejection fraction in obesity, whereas recent studies examining global
longitudinal strain show an association of BMI and central adiposity with LV systolic dysfunction using this more sensitive measure.26-28 Our study extends these findings to a large community-based population of middle-aged and older adults and demonstrates a robust association of BMI and central adiposity with global longitudinal strain. Further, our results support an association of metabolic phenotypes, including insulin resistance and hypertriglyceridemia with strain measures, above and beyond obesity itself.

Of note, we show a distinct association of BMI, central adiposity, insulin resistance, and hypertriglyceridemia with global longitudinal strain, whereas there were no significant associations with circumferential strain. This mirrors the early decline in longitudinal deformation with relative preservation of radial deformation in models of ischemia and increased afterload states.29,30 In addition, we found that diastolic function as assessed by mitral inflow E/e' ratio correlated with worse longitudinal and better circumferential strain. Indeed, increasing left atrial to LV gradients in an animal model of pacing-induced heart failure result in greater diastolic lengthening rate of the LV in the anteroposterior and septolateral dimensions but progressive decline in long-axis lengthening.31

Of note, diabetes mellitus was associated with circumferential but not longitudinal strain after adjusting for BMI. Interestingly, circumferential strain previously was found to be more strongly predictive of incident heart failure compared with longitudinal strain.13 These results are distinct from previous analyses from the ARIC study (Atherosclerosis Risk in the Community), which showed an association of dysglycemia and diabetes mellitus with global longitudinal strain.32 This difference in results may be because of the older mean age of the ARIC participants compared with our study population. Cardiac effects of age-related changes in body composition are often difficult to separate from inherent effects of obesity,33 and it may be that in our younger cohort, we observe more direct associations of cardiometabolic dysfunction on cardiovascular phenotypes, whereas in older samples, age-related effects may be at play. In fact, an earlier study on a subsample of older FHS participants showed a similar association of diabetes mellitus with longitudinal strain,23 which we no longer observe in a younger sample with more than double the number of participants, and after accounting for BMI differences.

The mechanisms underlying obesity-associated cardiac remodeling are likely multifaceted. Previous experimental studies support the potential role of circulating adipose-derived hormones. For example, circulating leptin can have direct myocardial effects on fatty acid metabolism, hypertrophy, and fibrosis and may also influence cardiac function indirectly via vascular and hypothalamic effects.34 Soluble leptin receptor is the predominant leptin-binding protein in the blood and thus may directly modulate leptin action.34 Circulating adiponectin binds to adiponectin receptor 1 on cardiac myocytes, with downstream cardioprotective effects on cardiac fatty acid and glucose metabolism, hypertrophy, fibrosis, and apoptosis.35 We found that circulating leptin but not adiponectin concentrations were associated with global longitudinal strain. Interestingly, previous studies have suggested that leptin may be linked to increased aldosterone secretion.35 However, leptin remained associated with longitudinal strain even after adjusting for aldosterone concentrations, and there was no association of aldosterone or the aldosterone-to-renin ratio and measures of LV strain. Similarly, we did not find an association of C-reactive protein and measures of cardiac strain.
Previous population-based data show that higher leptin concentrations are associated with diastolic dysfunction.\textsuperscript{36} We now extend previous findings to also highlight a role for leptin in relation to LV systolic mechanics in humans, which corroborates previous findings in leptin receptor–deficient animal models.\textsuperscript{37} It is important to note that data linking circulating leptin concentrations to clinical outcomes in population-based studies have shown conflicting results, with some studies suggesting higher risk and others a null or even protective effect.\textsuperscript{38–40}

Several limitations of our study should be considered. The observational, cross-sectional nature of our study precludes causal inferences, and the clinical value of strain measures remains unclear. Although strain measures have been associated with cardiovascular events among Framingham participants,\textsuperscript{13} these analyses were limited in power, and further studies are needed to elucidate clinical implications. We acknowledge that effect sizes were modest in our study and that the clinical significance of observed associations remains unclear. Specifically, although strain measures have been shown to improve with interventions such as bariatric surgery, exercise training, and spironolactone therapy in small trials of select patient groups with cardiometabolic disease,\textsuperscript{41–43} the clinical impact of improving LV systolic mechanics with regard to disease prevention remain unknown. We measured radial strain along 2 different imaging planes (short-axis and apical views) and note that the unknown. We measured radial strain along 2 different images have been obtained without specific focus on optimal endocardial border definition. However, image quality was acceptable for the vast majority of participants, and reproducibility was good for strain measures across different planes.\textsuperscript{44} It would have been interesting to examine pericardial fat depots; however, this was not assessed contemporaneous with strain measures, given variability in echocardiographic images. Finally, our study sample was predominantly white, limiting potential generalizability to other populations.

In sum, our findings highlight the association of central obesity and related cardiometabolic phenotypes above and beyond BMI with subclinical measures of LV systolic function and mechanics. We also found that obesity-related traits were associated with distinct aspects of LV mechanics, suggesting potential differential effects along specific LV planes of deformation. Finally, leptin was associated with global longitudinal strain, suggesting a potential role for circulating adipokines in obesity-related cardiac remodeling. Further work is needed to investigate the possible mechanisms underlying the link between cardiometabolic traits and subclinical alterations in cardiac mechanical dysfunction.

Sources of Funding
This work was partially supported by the National Heart, Lung and Blood Institute’s Framingham Heart Study (contracts N01-HC-25195 and HHSN268201500001I). Dr Ho is supported by National Institutes of Health (NIH) grant K23-HL116780 and the MGH Hassenfeld Scholar Award. Dr Cheng is supported in part by R00-HL-107642, R01-HL131532, R01-HL134168, and a grant from the Ellison Foundation. Dr Tsao is supported by K23-HL118259. Dr Benjamin was supported by R01-HL128914, R01-HL076784, and R01-AG028321.

Disclosures
None.


### CLINICAL PERSPECTIVE

Obesity and cardiometabolic dysfunction are associated with increased risk of heart failure and other cardiovascular diseases. We evaluated the associations of obesity-related phenotypes with echocardiographic measures of left ventricular mechanical function among 6231 participants of the Framingham Heart Study. Greater body mass index and central adiposity were associated with worse global longitudinal strain and synchrony. Measures of insulin resistance, dyslipidemia, and diabetes mellitus also were associated with distinct aspects of left ventricular mechanical function. Our findings highlight the association of central obesity and related cardiometabolic phenotypes above and beyond body mass index with subclinical measures of left ventricular mechanical function and may shed light onto obesity-related cardiac remodeling and heart failure.
Supplemental Material

Ho JE et al, Cardiometabolic Traits and Systolic Mechanics in the Community
**Supplemental Table 1.** Association of strain measures and clinical traits after additional adjustment for waist circumference and fasting glucose.

<table>
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<th>Echo measure</th>
<th>Clinical Trait</th>
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<th>Multivariable model with WC and FG*</th>
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<td>P</td>
<td>estimate (s.e.)</td>
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<td>Leptin</td>
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**Supplemental Table 2.** Associations of cardiometabolic traits and strain parameters, before and after accounting for sibling correlations

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<tr>
<td>Leptin receptor</td>
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Beta estimate represents the change in echo variable (strain expressed in %) per 1-standard deviation change in continuous clinical traits, and for the presence versus absence of dichotomous traits. Multivariable model adjusted for age, sex, body mass index, heart rate, systolic blood pressure, hypertension treatment, diabetes mellitus, HDL cholesterol, triglyceride concentrations. Biomarkers are log-transformed.