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Comorbidities and Cardiometabolic Disease

Relationship With Longitudinal Changes in Diastolic Function

Matthew Nayor, MD, MPH,[a,b] Danielle M. Enserro, PhD,[c] Vanessa Xanthakis, PhD,[a,d,e] Martin G. Larson, SD,[a,e] Emelia J. Benjamin, MD, ScM,[a,c,f] Jayashri Aragam, MD,[g,h] Gary F. Mitchell, MD,[i] Ramachandran S. Vasan, MD[a,d,f]

ABSTRACT

OBJECTIVES This study sought to evaluate the course, correlates, and prognosis of longitudinal changes in left ventricular (LV) diastolic dysfunction (DD) in the community-based Framingham Heart Study.

BACKGROUND Relationships of clinical risk factors to longitudinal progression of DD are incompletely understood.

METHODS Diastolic function was assessed by echocardiography performed at consecutive examinations (visits 1 and 2, mean interval 5.6 years) in 1,740 participants (64 ± 8 years of age at visit 1, 59% women) with normal LV systolic function and no atrial fibrillation.

RESULTS Of 1,615 individuals with normal-to-mild DD at visit 1, 198 (12%) progressed to ≥ moderate DD at visit 2. Progression was more likely in women and with advancing age ($p < 0.0001$). Of 125 individuals with ≥ moderate DD at visit 1, 25 (20%) regressed to normal-to-mild DD by visit 2. Regression of DD was associated with younger age ($p < 0.03$). In stepwise regression models, age, female sex, baseline and changes in systolic blood pressure, diastolic blood pressure, body mass index, serum triglycerides, and diabetes were positively associated with worsening diastolic function (all $p < 0.05$). Noncardiac comorbidity tracked with progressive DD. Cardiovascular disease (CVD) or death events occurred in 44 of 1,509 participants free of CVD at visit 2, during 2.7 ± 0.6 years of post-visit 2 follow-up. Presence of ≥ moderate DD was associated with higher risk (age- and sex-adjusted hazard ratio for CVD or death: 2.14; 95% confidence interval: 1.06 to 4.32; $p = 0.03$).

CONCLUSIONS In a community-based cohort of middle-aged to older adults, cardiometabolic risk factors and noncardiac comorbidities were associated with DD progression. Moderate or worse DD was associated with higher risk of CVD or death. (J Am Coll Cardiol HF 2018;6:317–25) © 2018 by the American College of Cardiology Foundation.

Left ventricular (LV) diastolic dysfunction (DD) may represent an intermediate stage in the development of cardiovascular disease (CVD) in older individuals and is associated with a number of conditions including heart failure (HF) (1-4), atrial fibrillation (5,6), and cardiovascular mortality (7,8). The pathophysiological link between LV DD and HF with preserved ejection fraction (HFpEF) is

From the [a]Framingham Heart Study, Framingham, Massachusetts; [b]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [c]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts; [d]Section of Preventive Medicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; [e]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; [f]Cardiology Section, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; [g]Cardiovascular Division, Veterans Administration Hospital, West Roxbury, Massachusetts; [h]Harvard Medical School, Boston, Massachusetts; and [i]Cardiovascular Engineering, Inc., Norwood, Massachusetts. Supported by National Heart, Lung, and Blood Institute (NHLBI) Framingham Heart Study contracts N01-HC-25195 and HHSN268201500001I; grants HL076784, G028321, HL070100, HL060040, HL080124, HL071039, HL077447, HL107385, HL126136, 2R01HL092577, 1R01HL128914, 1P50HL120163, and 2-K24-HL04334. Dr. Nayor is supported by NHLBI grant K23-HL138260 and training grant U10HL110337. Dr. Cooper is supported by the United Negro College Fund/Merck Science Initiative. Dr. Vasan is supported by an Evans Scholar award and the Jay and Louis Coffman Foundation from the Department of Medicine, Boston University School of Medicine. Dr. Mitchell owns Cardiovascular Engineering, Inc.; and has received grants and honoraria from and is a consultant for Novartis, Merck Sharp and Dohme, Servier, and Philips Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CRP = C-reactive protein

CVD = cardiovascular disease

DD = diastolic dysfunction

eGFR = estimated glomerular filtration rate

FEV_1 = forced expiratory volume in 1 s

FVC = forced vital capacity

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

particularly strong as progression of subclinical DD is thought to contribute to the pathogenesis of the syndrome (9). HFpEF currently accounts for approximately one-half of new HF diagnoses, and its prevalence relative to HF with reduced ejection fraction (HFrEF) continues to rise (10). As treatment options for HFpEF remain limited (11), despite its considerable morbidity and mortality (12), prevention of HFpEF is vital to individual and population health. Hence, it is critical to understand factors that contribute to the development and progression of LV DD.

Several previous reports have demonstrated the associations of LV DD with modifiable cardiometabolic risk factors such as blood pressure and body mass index (BMI) (13,14). However, strong relationships between age and LV DD and risk factor burden may partially obscure cross-sectional associations between LV DD and risk factors (15–18). Examining relationships of cardiometabolic traits with longitudinal changes in diastolic function measurements may, thus, provide further insight into key contributors to the progression of DD. In addition to conventional cardiovascular risk factors, noncardiac comorbidity—such as chronic kidney disease, chronic lung disease, musculoskeletal weakness, generalized systemic inflammation, and frailty—also predates HF and appears closely related to the development and the prognosis of HFpEF. (2,19,20). The association of noncardiac comorbidity with the longitudinal progression of LV DD has not been well elucidated.

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Accordingly, we sought to evaluate the course, predictors (both cardiac and noncardiac), and prognostic significance of longitudinal changes in LV diastolic function over a 6-year period in a moderately sized community-based cohort consisting of individuals mostly 60 to 70 years of age, when CVD incidence accelerates. We hypothesized that prevalent and worsening cardiometabolic risk factors and comorbidity burden are positively associated with adverse changes in common echocardiographic measurements of LV diastolic function and that worsening LV DD over time was associated with a higher risk of future CVD.

METHODS

STUDY SAMPLE. The design and enrollment of the Framingham Offspring and Omni Generation 1 cohorts have been detailed previously (21,22). We included Framingham Offspring participants who attended both the 8th (2005 to 2008, visit 1) and the 9th (2011 to 2014, visit 2) examination cycles and Omni Generation 1 participants who attended their 3rd (2007 to 2008, visit 1) and 4th (2011 to 2014, visit 2) examinations. From 2,478 participants attending both examinations, we excluded individuals missing LV diastolic function indices (n = 290), baseline LV wall motion abnormalities (n = 78), interim myocardial infarction between examinations (n = 43), LV systolic dysfunction (defined as fractional shortening ≤0.29 or 2-dimensional [2D] evidence of ≥ mild LV systolic dysfunction [n = 21]), ≥ moderate valvular disease (n = 105), paced rhythm (n = 18), atrial fibrillation at the time of echocardiography (n = 2), or missing covariates (n = 181). The final sample of 1,740 was used to evaluate predictors of longitudinal changes in LV diastolic function. To evaluate associations of noncardiac comorbidities with DD progression, we excluded an additional 339 individuals whose data were missing comorbidity measurements. For prospective analyses relating longitudinal changes in diastolic function with incident CVD, we excluded participants with prevalent CVD at visit 2 (n = 231) (Online Figure 1). All participants provided informed consent, and the Boston University Medical Center Institutional Review Board approved all study protocols.

ECHOCARDIOGRAPHY. Two-dimensional echocardiography with Doppler color flow imaging was performed at both examination visits (details in Online Appendix). We characterized LV diastolic function as normal, mild DD, moderate DD, or severe DD by using modified Olmsted criteria (excluding mitral inflow velocities during the Valsalva maneuver and pulmonary venous flow patterns, which were not available for the present investigation) (7,23). The following criteria were used: *normal* LV diastolic function: E/A >0.75 and E/E′ <10; *mild DD*, E/A ≤0.75 and E/E′ <10; *moderate DD*, E/A ≤1.5 and E/E′ ≥10; and *severe DD*, E/A >1.5 and E/E′ ≥10.

COVARIATES. A comprehensive medical history, a clinical examination focused on cardiovascular health, anthropometry, and phlebotomy were performed at each Framingham Heart Study examination. Details of the assessment of clinical covariates are provided in Online Appendix.

COMORBIDITY ASSESSMENT AND SCORE. Select measurements representing kidney (estimated glomerular filtration rate [eGFR]) and lung (forced expiratory volume in 1 s [FEV_1]-to-forced vital capacity [FVC] ratio) functions, musculoskeletal weakness (handgrip), frailty (gait speed), and general